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AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Division of the American Chemical Society, Polskie Towarzystwo Chemiczne, Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. The hard cover edition is published by John Wiley and Sons, Inc., in the traditional format, and it differs in content primarily by the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Incorporation of graphical abstracts into the Table of Contents began with Volume 77. Annual volumes 70–74 and 75–79 have been incorporated into five-year versions of the collective volumes of *Organic Syntheses* that appeared as Collective Volume IX and X in the traditional hard cover format, available for purchase from the publishers. The Editors hope that the new Collective Volume series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

Organic Syntheses, Inc., joined the age of electronic publication in 2001 with the release of its free web site (www.orgsyn.org) followed in 2003 with the completion of a commercially available electronic database (www.mrw.interscience.wiley.com/osdb). Organic Syntheses, Inc., fully funded the creation of the free website at www.orgsyn.org in a partnership with CambridgeSoft Corporation and Data-Trace Publishing Company. The site is accessible to most internet browsers using Macintosh and Windows operating systems and may be used with or without a ChemDraw plugin. Because of continually evolving system requirements, users should review software compatibility at the

website prior to use. John Wiley & Sons, Inc., and Accelrys, Inc., partnered with Organic Syntheses, Inc., to develop the new database (www.mrw.interscience.wiley.com/osdb) that is available for licensing from John Wiley & Sons, Inc.

Both the commercial database and the free website contain all annual and collective volumes and indices of *Organic Syntheses*. Chemists can draw structural queries and combine structural or reaction transformation queries with full-text and bibliographic search terms, such as chemical name, reagents, molecular formula, apparatus, or even hazard warnings or phrases. The preparations are categorized into reaction types, allowing search by category. The contents of individual or collective volumes can be browsed by lists of titles, submitters' names, and volume and page references, with or without reaction equations.

The commercial database at www.interscience.wiley.com/db/os also enables the user to choose his/her preferred chemical drawing package, or to utilize several freely available plug-ins for entering queries. The user is also able to cut and paste existing structures and reactions directly into the structure search query or their preferred chemistry editor, streamlining workflow. Additionally, this database contains links to the full text of primary literature references via CrossRef, ChemPort, Medline, and ISI Web of Science. Links to local holdings for institutions using open url technology can also be enabled. The database user can limit his/her search to, or ordered the search results by, such factors as reaction type, percentage yield, temperature, and publication date, and can create a customized table of reactions for comparison. Connections to other Wiley references are currently made via text search. Incorporations of new preparations will occur as new material becomes available.

INFORMATION FOR AUTHORS OF PROCEDURES

Organic Syntheses welcomes and encourages submissions of experimental procedures that lead to compounds of wide interest or that illustrate important new developments in methodology. Proposals for *Organic Syntheses* procedures will be considered by the Editorial Board upon receipt of an outline proposal as described below. A full procedure will then be invited for those proposals determined to be of sufficient interest. These full procedures will be evaluated by the Editorial Board, and if approved, assigned to a member of the Board for checking. In order for a procedure to be accepted for publication, each reaction must be successfully repeated in the laboratory of a member of the Editorial Board at least twice, with similar yields (generally $\pm 5\%$) and selectivity to that reported by the submitters.

Organic Syntheses Proposals

A cover sheet should be included providing full contact information for the principal author and including a scheme outlining the proposed reactions (an Organic Syntheses Proposal Cover Sheet can be downloaded from the *Organic Syntheses* websites). Attach an outline proposal describing the utility of the methodology and/or the usefulness of the product. Identify and reference the best current alternatives. For each step, indicate the proposed scale, yield, method of isolation and purification, and how the purity of the product is determined. Describe any unusual apparatus or techniques required, and any special hazards associated with the procedure. Identify the source of starting materials. Enclose copies of relevant publications (attach pdf files if an electronic submission is used).

Submit proposals by mail or as email attachments to:

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Submission of Procedures

Authors invited by the Editorial Board to submit full procedures should prepare their manuscripts in accord with the Instructions to Authors which may be obtained from the Associate Editor or downloaded from the *Organic Syntheses* websites. Submitters are also encouraged to consult earlier volumes of *Organic Syntheses* for models with regard to style, format, and the level of experimental detail expected in *Organic Syntheses* procedures. Manuscripts should be submitted in triplicate to the Associate Editor. Electronic submissions are encouraged; procedures will be accepted as e-mail attachments in the form of Microsoft Word files with all schemes and graphics also sent separately as ChemDraw files.

Procedures that do not conform to the Instructions to Authors with regard to experimental style and detail will be returned to authors for correction. Authors will be notified when their manuscript is approved for checking by the Editorial Board, and it is the goal of the Board to complete the checking of procedures within a period of no more than six months.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Associate Editor. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Volume Editor felt was more

appropriate. The Chemical Abstracts indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic Chemical Abstracts nomenclature, used in the Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Chemical Abstracts Registry numbers, which are useful in computer searching and identification, are also provided in these appendices. Whenever two names are concurrently in use and one name is the correct Chemical Abstracts name, that name is preferred.

ACKNOWLEDGMENT

Organic Syntheses wishes to acknowledge the contributions of Merck & Co. and Pfizer, Inc. to the success of this enterprise through their support, in the form of time and expenses, of members of the Board of Editors.

HANDLING HAZARDOUS CHEMICALS

A Brief Introduction

General Reference: *Prudent Practices in the Laboratory*; National Academy Press; Washington, DC, 1995.

Physical Hazards

Fire. Avoid open flames by use of electric heaters. Limit the quantity of flammable liquids stored in the laboratory. Motors should be of the nonsparking induction type.

Explosion. Use shielding when working with explosive classes such as acetylides, azides, ozonides, and peroxides. Peroxidizable substances such as ethers and alkenes, when stored for a long time, should be tested for peroxides before use. Only sparkless “flammable storage” refrigerators should be used in laboratories.

Electric Shock. Use 3-prong grounded electrical equipment if possible.

Chemical Hazards

Because all chemicals are toxic under some conditions, and relatively few have been thoroughly tested, it is good strategy to minimize exposure to all chemicals. In practice this means having a good, properly installed hood; checking its performance periodically; using it properly; carrying out all operations in the hood; protecting the eyes; and, since many chemicals can penetrate the skin, avoiding skin contact by use of gloves and other protective clothing at all times.

a. Acute Effects. These effects occur soon after exposure. The effects include burn, inflammation, allergic responses, damage to the eyes, lungs, or nervous system (e.g., dizziness), and unconsciousness or death (as from overexposure to HCN). The effect and its cause are usually obvious and so are the methods to prevent it. They generally arise from inhalation or skin contact, so should not be a problem if one follows

the admonition “work in a hood and keep chemicals off your hands”. Ingestion is a rare route, being generally the result of eating in the laboratory or not washing hands before eating.

b. Chronic Effects. These effects occur after a long period of exposure or after a long latency period and may show up in any of numerous organs. Of the chronic effects of chemicals, cancer has received the most attention lately. Several dozen chemicals have been demonstrated to be carcinogenic in man and hundreds to be carcinogenic to animals. Although there is no simple correlation between carcinogenicity in animals and in man, there is little doubt that a significant proportion of the chemicals used in laboratories have some potential for carcinogenicity in man. For this and other reasons, chemists should employ good practices at all times.

The key to safe handling of chemicals is a good, properly installed hood, and the referenced book devotes many pages to hoods and ventilation. It recommends that in a laboratory where people spend much of their time working with chemicals there should be a hood for each two people, and each should have at least 2.5 linear feet (0.75 meter) of working space at it. Hoods are more than just devices to keep undesirable vapors from the laboratory atmosphere. When closed they provide a protective barrier between chemists and chemical operations, and they are a good containment device for spills. Portable shields can be a useful supplement to hoods, or can be an alternative for hazards of limited severity, e.g., for small-scale operations with oxidizing or explosive chemicals.

Specialized equipment can minimize exposure to the hazards of laboratory operations. Impact resistant safety glasses are basic equipment and should be worn at all times. They may be supplemented by face shields or goggles for particular operations, such as pouring corrosive liquids. Because skin contact with chemicals can lead to skin irritation or sensitization or, through absorption, to effects on internal organs, protective gloves should be worn at all times.

Laboratories should have fire extinguishers and safety showers. Respirators should be available for emergencies. Emergency equipment should be kept in a central location and must be inspected periodically.

MSDS (Materials Safety Data Sheets) sheets are available from the suppliers of commercially available reagents, solvents, and other chemical materials; anyone performing an experiment should check these data sheets before initiating an experiment to learn of any specific hazards associated with the chemicals being used in that experiment.

DISPOSAL OF CHEMICAL WASTE

General Reference: *Prudent Practices in the Laboratory* National Academy Press, Washington, D.C. 1996

Effluents from synthetic organic chemistry fall into the following categories:

1. Gases

- 1a. Gaseous materials either used or generated in an organic reaction.
- 1b. Solvent vapors generated in reactions swept with an inert gas and during solvent stripping operations.
- 1c. Vapors from volatile reagents, intermediates and products.

2. Liquids

- 2a. Waste solvents and solvent solutions of organic solids (see item 3b).
- 2b. Aqueous layers from reaction work-up containing volatile organic solvents.
- 2c. Aqueous waste containing non-volatile organic materials.
- 2d. Aqueous waste containing inorganic materials.

3. Solids

- 3a. Metal salts and other inorganic materials.
- 3b. Organic residues (tars) and other unwanted organic materials.
- 3c. Used silica gel, charcoal, filter aids, spent catalysts and the like.

The operation of industrial scale synthetic organic chemistry in an environmentally acceptable manner* requires that all these effluent categories be dealt with properly. In small scale operations in a research or

*An environmentally acceptable manner may be defined as being both in compliance with all relevant state and federal environmental regulations *and* in accord with the common sense and good judgement of an environmentally aware professional.

academic setting, provision should be made for dealing with the more environmentally offensive categories.

- 1a. Gaseous materials that are toxic or noxious, e.g., halogens, hydrogen halides, hydrogen sulfide, ammonia, hydrogen cyanide, phosphine, nitrogen oxides, metal carbonyls, and the like.
- 1c. Vapors from noxious volatile organic compounds, e.g., mercaptans, sulfides, volatile amines, acrolein, acrylates, and the like.
- 2a. All waste solvents and solvent solutions of organic waste.
- 2c. Aqueous waste containing dissolved organic material known to be toxic.
- 2d. Aqueous waste containing dissolved inorganic material known to be toxic, particularly compounds of metals such as arsenic, beryllium, chromium, lead, manganese, mercury, nickel, and selenium.
3. All types of solid chemical waste.

Statutory procedures for waste and effluent management take precedence over any other methods. However, for operations in which compliance with statutory regulations is exempt or inapplicable because of scale or other circumstances, the following suggestions may be helpful.

Gases

Noxious gases and vapors from volatile compounds are best dealt with at the point of generation by “scrubbing” the effluent gas. The gas being swept from a reaction set-up is led through tubing to a (large!) trap to prevent suck-back and into a sintered glass gas dispersion tube immersed in the scrubbing fluid. A bleach container can be conveniently used as a vessel for the scrubbing fluid. The nature of the effluent determines which of four common fluids should be used: dilute sulfuric acid, dilute alkali or sodium carbonate solution, laundry bleach when an oxidizing scrubber is needed, and sodium thiosulfate solution or diluted alkaline sodium borohydride when a reducing scrubber is needed. Ice should be added if an exotherm is anticipated.

Larger scale operations may require the use of a pH meter or starch/iodide test paper to ensure that the scrubbing capacity is not being exceeded.

When the operation is complete, the contents of the scrubber can be poured down the laboratory sink with a large excess (10–100 volumes) of water. If the solution is a large volume of dilute acid or base, it should be neutralized before being poured down the sink.

Liquids

Every laboratory should be equipped with a waste solvent containers in which *all* waste solvents and solutions are collected. Incompatible materials should be collected in separate containers. Waste containers should be properly labeled, should be sealed when waste is not being added, and should be stored in a secondary container.

Arrangements should be made for contracted disposal in a regulated and licensed incineration facility.

Solids

In general, organic and inorganic solid waste is treated as described above for liquid waste. Inorganic solid wastes, particularly those containing toxic metals and toxic metal compounds, used Raney nickel, manganese dioxide, etc. should be placed in glass bottles or lined fiber drums, sealed, properly labeled, and arrangements made for disposal in a secure landfill.** Used mercury is particularly pernicious and small amounts should first be amalgamated with zinc or combined with excess sulfur to solidify the material.

Other types of solid laboratory waste including used silica gel and charcoal should also be packed, labeled, and sent for disposal in a secure landfill.

Special Note

Since local ordinances may vary widely from one locale to another, one should always check with appropriate authorities. Also, professional disposal services differ in their requirements for segregating and packaging waste.

**If arrangements for incineration of waste solvent and disposal of solid chemical waste by licensed contract disposal services are not in place, a list of providers of such services should be available from a state or local office of environmental protection.

DEDICATION



The Members of the Corporation of Organic Syntheses, Inc. dedicate Volume 83 of *Organic Syntheses* to Professor Jeremiah P. Freeman of the University of Notre Dame as a token of thanks for his tireless efforts as Secretary of the Board of Editors, Secretary of the Board of Directors, and Secretary of the Corporation of Organic Syntheses. Over a quarter of a century from 1979 until his retirement as Secretary in 2004, Jerry was Org Syn. He handled everything from ordering the beignets and coffee at the Board Meetings, to handling all of the

Corporation's correspondence, to editing the Collective Volumes and overseeing the transition to the web. Jerry leaves behind an enduring mark on both the publication and the Corporation. We congratulate him on his accomplishments and wish him well going forward.

AUTOBIOGRAPHY BY JEREMIAH P. FREEMAN



Professional Life

My adventures in chemistry began in high school when I had a crude lab in the basement of my home. My father owned a drug store and I was able to obtain chemicals through his suppliers. I was fascinated by the signs of chemical change: color, precipitates, sounds (the sensory side of chemistry). My real introduction to research was in my senior year (1949–1950) at Notre Dame where I was informed by the Assistant

Chairman of the chemistry department that I was to do senior research with Professor Ernest Eliel, a relatively new member of the faculty. (You will notice from this brief introduction what a different world I grew up in: I could order chemicals easily and I was told what to do as a student!)

My research project with Professor Eliel was to examine the stereochemistry of the reduction of an optically active halide with the new reducing agent, lithium aluminum hydride. In order to obtain such a halide that would be subject to reduction without concurrent elimination, we prepared optically active α -chloro- α -phenylpropionic acid. This involved the preparation of atrolactic acid, its resolution using quinine, and replacement of the hydroxy group with halogen. The preparation of the acid involved the formation of acetophenone cyanohydrin and its subsequent hydrolysis. (This procedure, after extensive polishing by Professor Eliel, was submitted to *Organic Syntheses* and appeared in Volume 33 of that series. This was my first experience with this publication, which was to become an important part of my later scientific life.) Unfortunately, I could not obtain the chloroacid optically pure, but we could establish that the reduction had occurred principally by inversion at the chiral center. (This work, after considerable further investigation by Professor Eliel, was published in the *Journal of the American Chemical Society* in 1952.)

Professor Eliel introduced me to research and emphasized to me that it does not always proceed the way it is planned and that it is important to identify all the products of a reaction, not just those we were expecting. This experience was eye opening for me.

Through the help of Professor Eliel and of Professor Charles Price, the chairman of the department, I was admitted for graduate work at the University of Illinois, with which both of them had been associated. I joined the research group of Professor R. C. Fuson. Since the war in Korea had begun just before I entered Illinois, I opted to write an MS thesis based upon my first year of research in case I was drafted. (Fortunately for me at least, the government still deferred students in those days and I was able to pursue my PhD work.)

I took up a problem that had been pioneered by Bill Emmons as he finished up his own PhD work. (Professor Fuson very often encouraged his senior graduate students to pursue their own ideas in his research area; often this opened up new problems for beginning researchers.) This was the beginning of a lifelong professional and personal association with Bill Emmons that proved to be a very important influence on my career.

Through Prof. Fuson's connections, I became acquainted with the work at the Redstone Arsenal Research Division of the Rohm and Haas Co. in Huntsville, AL. I decided to accept their offer of a job much to the horror of my fellow students, who wondered why anyone would want to live in rural Alabama. But it turned out to be a most important and correct decision for me. Bill Emmons was the head of the organic chemistry group of the Chemistry Section, whose objective was to synthesize novel compounds as either additives or binders for solid propellants, principally for use in shoulder-fired weapons ("bazookas"). Rohm and Haas Co. had no commercial interest in this area and were simply running the lab for the Army on a non-profit basis. At first the work involved the chemistry of nitrate esters, nitramines, and polynitro compounds. In order to get the lab known to the chemical community so that better and better people would be attracted to it, the company adopted a liberal publication policy, limited only by the restrictions imposed by DOD secrecy classifications. For the most part these were easily relaxed for our publications.

When Emmons moved to the R&H research laboratories in Philadelphia in 1957, I succeeded him as the organic group leader. Before Bill left, our research focus had changed to examining the chemistry of fluoronitrogen compounds at the direction of our new Chemistry Section head, Warren Niederhauser, later a president of the American Chemical Society. ("Thinking outside the box" was not a common expression in those days, but it certainly characterized Warren.) After some fits and false starts during which I injured my left hand in an explosion, our group discovered the reaction of tetrafluorohydrazine, N_2F_4 , only recently discovered by another group in our laboratories, with alkenes to produce *vic*-bis-difluoraminoalkanes, the first organic fluoronitrogen derivatives.

Subsequently, we examined the preparation of difluoramine from tetrafluorohydrazine and its reactions with aldehydes and ketones, which lead to *gem*-bis(difluoramino) compounds. Ultimately none of these compounds ever found use in propellants, but it is interesting that during this work we improved the old electrochemical process for the preparation of nitrogen trifluoride. This is used today in the commercial preparation of this compound, which is widely used in the semiconductor industry.

In the fall of 1963 I was approached by Professor Eliel, who was to become head of the department in January 1964, as to my interest in returning to Notre Dame for the spring semester in 1964 to help with

their teaching needs. Rohm and Haas management was very cooperative and I received a leave of absence for the spring period. Late in that semester one of Notre Dame's organic faculty was recruited to be chairman at the University of West Virginia. After I had returned to Huntsville, Eliel called me to offer me that opening. I have to say that I was pleased and flattered by the offer and did not need much time to decide to accept it. I was aided in my transition to the academic life by the award of an A. P. Sloan fellowship.

When thinking about what kind of research to undertake at Notre Dame, I knew that there was much to be done in the fluoronitrogen area, but I also realized the dangers inherent in that area. So I decided to pursue other interests in the area of organic nitrogen compounds, particularly those containing nitrogen in intermediate oxidation states. Nitrones, nitrimines, nitroso compounds, and such compounds in one form or another have been the basis of my research since then. When I came to Notre Dame, I assumed administrative responsibilities as Assistant Chairman. While these mostly involved student matters, they also included anything the chairman did not want to be bothered with! I held this position for six years and then was appointed chairman in 1970. For one reason or another, I was kept in that position until 1979. The seventies was a very tough time for chemistry as a whole (poor job opportunities, a shrinking graduate population, constricted research budgets) and in particular at ND where budgets were very tight. A new laboratory building originally planned in 1965, was not started until 1979 and finally completed in 1981. Much important ground was lost during this period. (Ernest Eliel decided to leave ND for a chair at the University of North Carolina in 1972.)

In 1969 I was elected to a five-year term as the Secretary-Treasurer of the Division of Organic Chemistry of the American Chemical Society and in 1973 I was elected Chairman of that Division. In 1979, I was elected to be the Secretary of Organic Syntheses, Inc., a job with both a scientific component (Secretary to the Board of Editors) and a more administrative component (Secretary to the Board of Directors). Historically, this position was for a ten-year term, at the end of which the retiring Secretary acted as Editor of a Collective Volume of this series. During my term, it was decided to go to five-year Collective Volumes. The two Boards also decided to retain me past the ten-year period and in all I served for twenty-five years which ended in 2004 at my instigation. During that period, I edited four of the five-year collective volumes and assembled a cumulative index of the first eight collective volumes.



Jerry Freeman in his role as Secretary of the Board of Editors

I really had a very stimulating and enjoyable job with Organic Syntheses. I met many interesting people; I particularly enjoyed my associations with foreign editors and those from the chemical industry.

The later stages of my research career were among the most satisfying due to my collaboration with two remarkable chemists who were both graduates of the American University of Beirut. One, an Arab, Mahluf Haddadin, came to Notre Dame as a Visiting Professor while on sabbatical from AUB in 1978–1979. During that time and subsequently, we published seven papers. To this day, I consider him to be one of my best friends, as do other members of my family.

The second, a Jew, Jacob Szmuszkovicz, had retired after a very productive career with the then Upjohn Co. in nearby Kalamazoo, MI. (I mention the combination of Arab and Jew to contrast the world of science where such ethnic differences are or ought to be unimportant with the world at large, which puts such pejorative emphasis on them). Jake became an adjunct professor at Notre Dame and taught a course in medicinal chemistry bi-annually. Based largely on extensions of his research in that area, our efforts led to nineteen publications. I am particularly proud of the fact that my publications spanned five decades, the last appearing in 2004.

During my years at Notre Dame, I came to realize that my greatest satisfaction was in determining the structures of unexpected products.

As spectroscopic and x-ray methods became more sophisticated and accessible, this area has become almost routine and only in extremely complex cases is it still a significant area of research. I think I retired at the right time.

While I have devoted much time to describing my research activities, I have to say that I derived my greatest satisfaction from undergraduate teaching. Most of my teaching involved the introductory course in organic chemistry populated principally by premedical students. While this was a large class and involved writing many letters of recommendation, I early recognized that I was dealing with many of the best students at Notre Dame, best in both the sense of very bright and hard working, but also in terms of their character. Most of them were idealistic, caring persons in the finest Christian sense. I have maintained a relationship with many of them to this day.

Personal Life

I was born in Detroit to an Irish family. All my grandparents, whom I never knew, and my father were born in Ireland; yet I was not raised as an Irishman, but as an American. I was educated in a Catholic elementary school and high school and at Notre Dame.

At Illinois, while I was a teaching assistant, I met Mary Miffin in one of the lab sections I was in charge of. Mary was in her sophomore year and was taking chemistry because she had changed her major that year to geology. Fortuitously, she chose to stay for the summer session to take physics, also required for her major. In this time, we got to know each other very well. We both graduated in June 1953 and were married at St. John's Chapel on the campus just before graduation. Our honeymoon consisted of a month long auto trip through the West.

We moved to Huntsville late that summer and had our first introduction to a southern summer. Despite the uncomfortable racial climate, we enjoyed our days in Huntsville. My colleagues at work were a very interesting and stimulating group, as were their spouses. In fact, Mary was not terribly enthusiastic when I decided to return to Notre Dame. During this time we had five children, four boys and a girl.

Life in South Bend has been pleasant. Our kids adapted to the winter weather and most of them learned to ski. Our sixth child, a girl was born here. In 1967 Mary decided that she wanted a life apart from that of a professor's wife. That summer she spent in Chicago getting certified as a Montessori teacher. After assisting at a local school she started her own school in the basement of our local parish, Little Flower. After

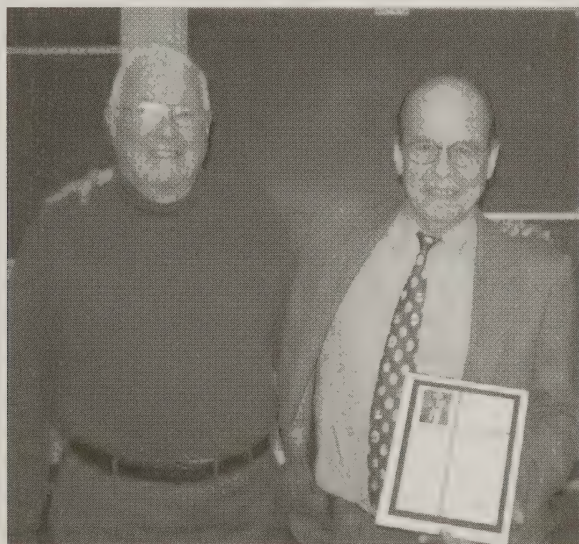
a couple of moves, and Katie's birth in 1970, she "retired" satisfied that she had accomplished when she had set out to do. Her school still exists, now as the Montessori Academy at Edison Lakes.

Five of our children are college graduates: three from Notre Dame, one from California, Berkeley and one from Indiana U. Two graduated from law school and one from medical school and two are professional surveyors. They are distributed all over the country: two in California, one in Nevada, one in Texas, one in North Carolina and one in Indiana. We now have fifteen grandchildren.

JEREMIAH P. FREEMAN

PREFACE

Last year marked the end of the 25-year “Freeman Era” of *Organic Syntheses*, so it is fitting that this volume be dedicated to Professor Jeremiah P. Freeman of the University of Notre Dame. Jerry ran the ship with a firm and efficient hand as Secretary of the Board of Editors, Secretary of the Board of Directors and Secretary of the Corporation. There’s more about Jerry elsewhere in the Volume, so here I simply take the opportunity to thank Jerry once more on behalf of the all the Corporation for his long and selfless service. A more formal thanks has already been expressed by helping Notre Dame to endow the “Jeremiah P. Freeman Organic Syntheses Lectureship”, and the first JPFORGSYN lecture was presented in April by Professor K. Barry Sharpless of the Scripps Research Institute. The only remaining challenge with this lectureship seems to be pronouncing the acronym – just try to say “JPFORGSYN” fast three times.



Jerry Freeman and K. Barry Sharpless, April 2006

In his preface to Volume 82, Ed Grabowski wished the new helmsmen, Rick Danheiser (Editor-in-Chief) and Chuck Zercher (Associate Editor), “calm seas and a prosperous voyage”. And indeed the “Danheiser/Zercher Era” is off to an auspicious start. Thanks to Rick, Chuck and the other editors, checking times for preparations (preps) have decreased significantly, and Volume 83 has many very fresh preps. The checking times are down to less than six months (often much less), and accepted preps are now published on the web on a quarterly basis. Only six of the preps in this volume are being freshly published with this Preface. The other 22 have been available on the web for some time. We hope that both current and prospective authors will appreciate this expedited treatment.

Rick and Chuck also led the overhaul of the “orgsyn.org” web site this year, and it is now much more modern and user friendly. It was always powerful, especially in search functions, and that power has not been sacrificed. *Organic Syntheses* has been a leader in open access (free) publication, first with its long time policy of providing free soft-cover copies of annual volumes to Organic Division members of chemical societies of several nations, and more recently with the orgsyn.org web site. This is a true open access site – every prep ever published in *Organic Syntheses* is available to anyone, anywhere, all the time. And there are no ads either! This is possible because Organic Syntheses, Inc. is a non-profit entity. Libraries and individuals have been buying *Organic Syntheses* for more than eight decades now. The Corporation has invested the proceeds wisely and in turn is now spending some of the income that is generated to give *Organic Syntheses* back to the community that purchased it in the first place.

Volume 83 contains an eclectic collection of 28 preparations that reflect many of the most topical research themes in the field. The synthesis of ligands for asymmetric reactions is an important theme that is reflected in a number of preps. **PREPARATION OF ENANTIOMERICALLY PURE (*R,R*)-BozPHOS** is described from readily available DuPHOS, and then the ligand is used in **PREPARATION OF ENANTIOMERICALLY ENRICHED (1*S*)-1-PHENYLPROPAN-1-AMINE HYDROCHLORIDE BY A CATALYTIC ADDITION OF DIORGANOZINC REAGENTS TO IMINES**. Other ligands and reagents for asymmetric synthesis are presented in **SYNTHESIS OF (–)-(*S,S*)-BIS(4-ISOPROPYLOXAZOLINE), (*R,R*)-2,2'-BISPYRROLIDINE AND (*S,S*)-2,2'-BISPYRROLIDINE: USEFUL LIGANDS FOR ASYMMETRIC SYNTHESIS, (*S*)-(+)-2,4,6-TRIMETHYLBENZENESULFINAMIDE, and SYNTHESIS OF**

(+)-(1*R*,2*S*,9*S*)-11-METHYL-7,11-DIAZATRICYCLO[7.3.1.0^{2,7}] TRIDECAHE, A (+)-SPARTEINE SURROGATE.

The catalytic reactions themselves are featured in **CATALYTIC ASYMMETRIC ACYLATION OF ALCOHOLS USING A CHIRAL 1,2-DIAMINE DERIVED FROM (*S*)-PROLINE: (1*S*,2*S*)-*trans*-1-BENZOYLOXY-2-BROMOCYCLOHEXANE, NICKEL-CATALYZED HOMOALLYLATION OF ALDEHYDES WITH 1,3-DIENES, PREPARATION OF (*S*)-METHYL GLYCIDATE VIA HYDROLYTIC KINETIC RESOLUTION, 2-SUBSTITUTED-1,3-CYCLOHEXADIENES BY INTERMOLECULAR, METHYLENE-FREE TANDEM ENYNE METATHESIS, and IRIIDIUM-CATALYZED *N*-HETEROCYCLIZATION OF PRIMARY AMINES WITH DIOLS: *N*-BENZYLPIPERIDINE.**

Topical oxidations are represented by **OXIDATION OF NEROL TO NERAL WITH IODOBENZENE DIACETATE AND TEMPO, and COPPER-CATALYZED ELECTROPHILIC AMINATION OF DIORGANOZINC REAGENTS: 4-PHENYL MORPHOLINE,** while boron-mediated allylations are the focus in **RADICAL ALLYLATION OF *B*-ALKYLCATECHOLBORANES and ALLYLBORONATION OF IMINES: 1-PHENYLHEX-5-EN-3-AMINE.**

Convenient functional group transformations include **DIRECT CHLORINATION OF ALCOHOLS: SYNTHESIS OF ETHYL 3-CHLORO-3-PHENYLPROPANOATE, AU(I)-CATALYZED HYDRATION OF ALKYNES: 2,8-NONANEDIONE, and the reductive etherification of a silyl ether to make 2-(2',2'-DIMETHYLPROPOXY)-2,3-DIHYDRO-1*H*-INDENE.**

Ubiquitous cross-coupling reactions are featured in **SUZUKI-MIYAUURA CROSS-COUPPLING: PREPARATION OF 2'-VINYL-ACETANILIDE,** while practical ring-forming reactions are represented by **FRAGMENTATION-RECOMBINATION NAZAROV CYCLIZATION: 3,4-DIMETHYLCYCLOPENT-2-EN-1-ONE, SYNTHESIS OF 2 α -BENZYLOXY-8-OXABICYCLO[3.2.1] OCT-6-EN-3-ONE BY [4 + 3] CYCLOADDITION, INDIUM-CATALYZED CYCLOISOMERIZATION: PREPARATION OF 4-METHYLPYRROLO[1,2-*a*] QUINOLINE, and TRIFLUOROMETHANESULFONIMIDE-CATALYZED (2 + 2)-CYCLOADDITION OF SILYL ENOL ETHERS WITH α,β -UNSATURATED ESTERS: 1-(*tert*-BUTYLDIMETHYLSILOXY)-8-(METHOXY-CARBONYL)-6-METHYLBICYCLO[4.2.0]OCTANE.**

Methods for making organofluorine molecules take center stage in **5-endo-trig-CYCLIZATION OF 1,1-DIFLUORO-1-ALKENES: SYNTHESIS OF 3-BUTYL-2-FLUORO-1-TOSYLINDOLE**, and **TRIFLUOROMETHYLATION AT THE α -POSITION OF α,β -UNSATURATED KETONES: 4-PHENYL-3-(TRIFLUOROMETHYL)BUTAN-2-ONE**.

A few preps also focus on useful or simply fascinating compounds like **SYNTHESIS OF 6,9,12,15,18-PENTAMETHYL-1,6,9,12,15,18-HEXAHYDRO(C₆₀-I_h)[5,6]FULLERENE**, **SYNTHESIS OF 2-CHLOROACROLEIN DIETHYL ACETAL**, and **SYNTHESIS OF DITHIENO[3,2-*b*:2',3'-*d*]THIOPHENE**.

In addition to thanking Rick and Chuck for all their help in putting this Volume together, I want to thank all my Co-editors at *Organic Syntheses* over the last eight years. I learned a great deal about experimental organic chemistry in our discussions, and I am more convinced than ever of the crucial role that *Organic Syntheses* plays in conveying experimental information to the synthesis community at large. Lastly, I thank all the checkers in the editors' labs and the submitters in the authors' labs. It is on the backs of these experimental chemists, often students, that this Volume and indeed the whole field are built.

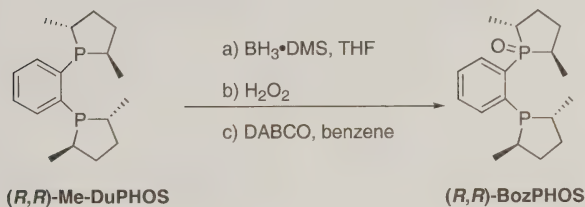
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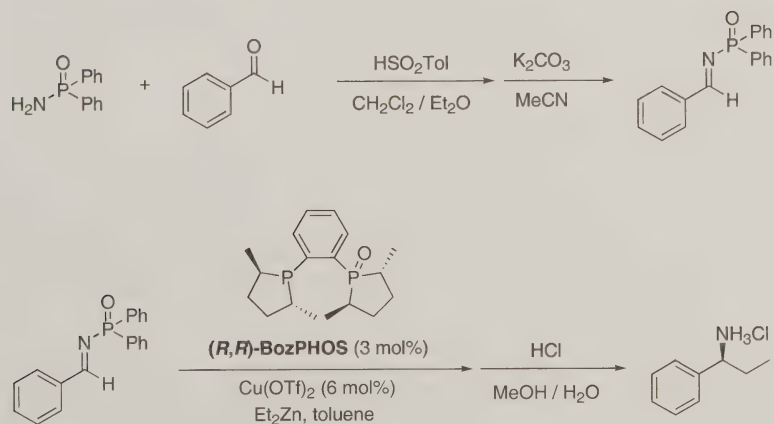
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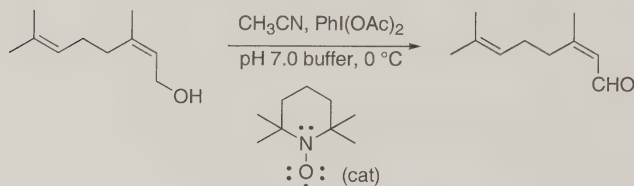
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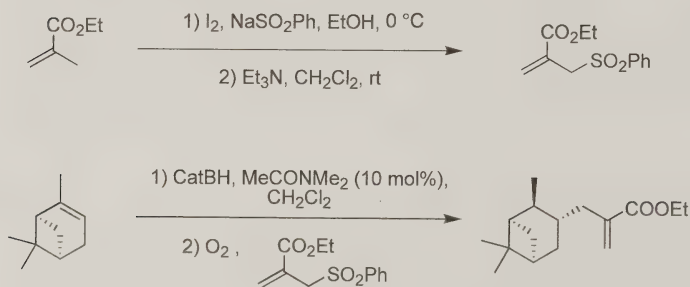
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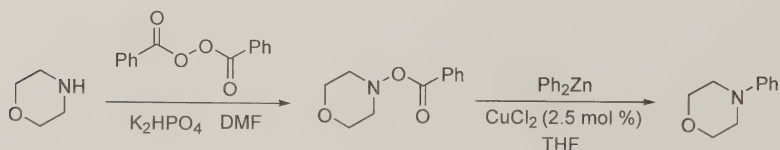
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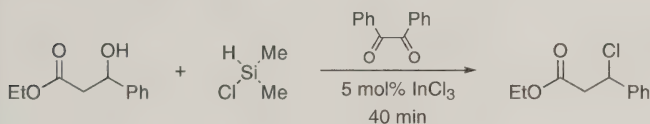
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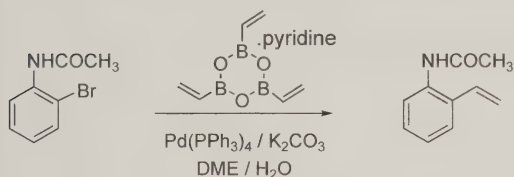
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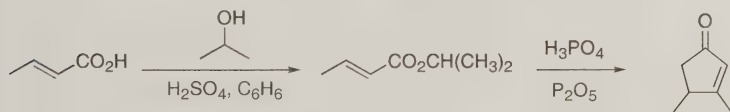
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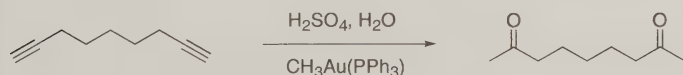
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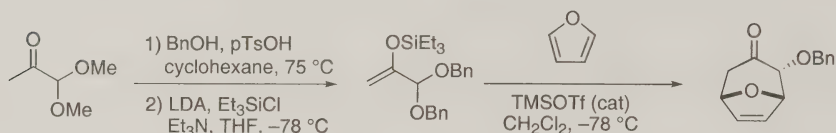
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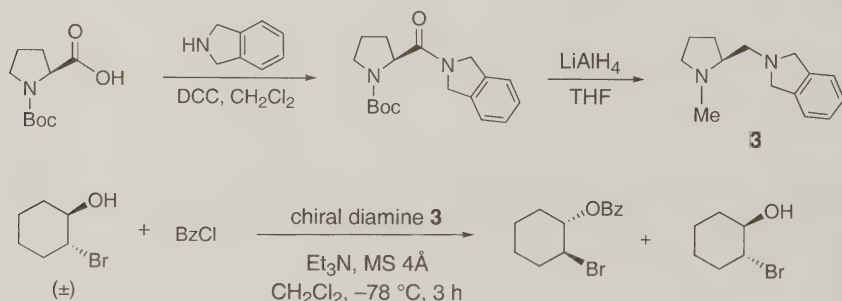
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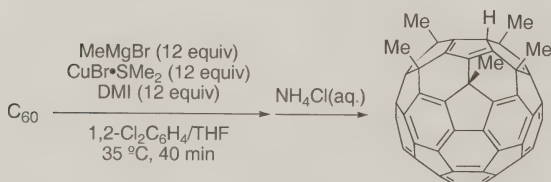
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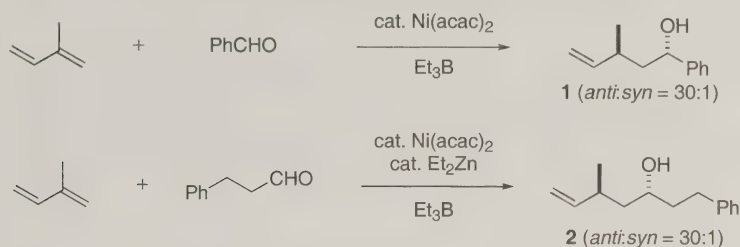
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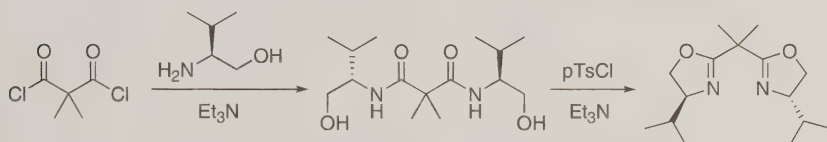
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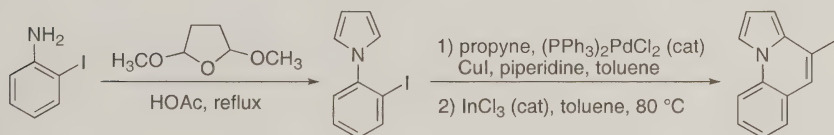
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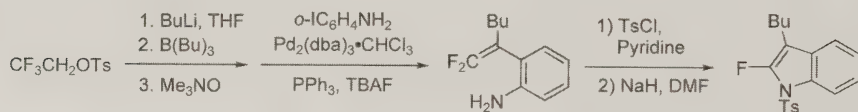
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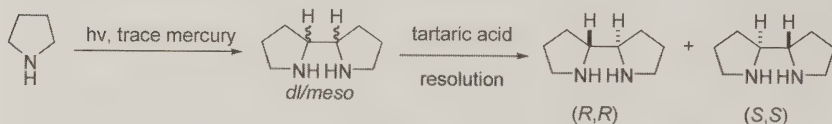
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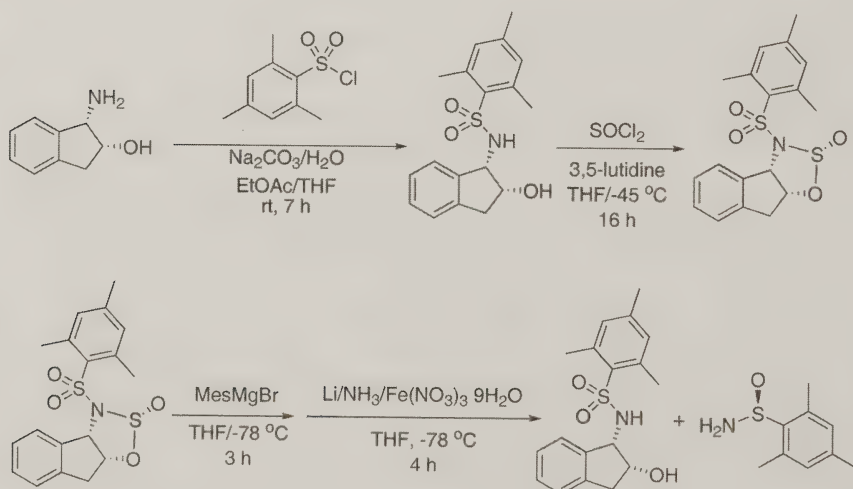
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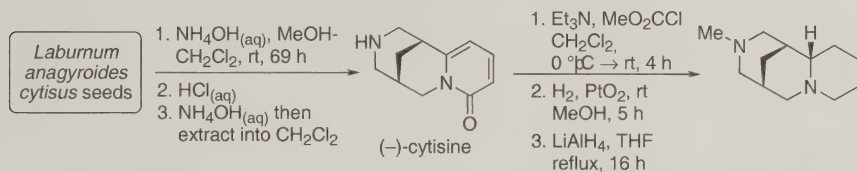
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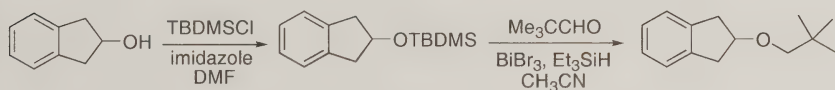
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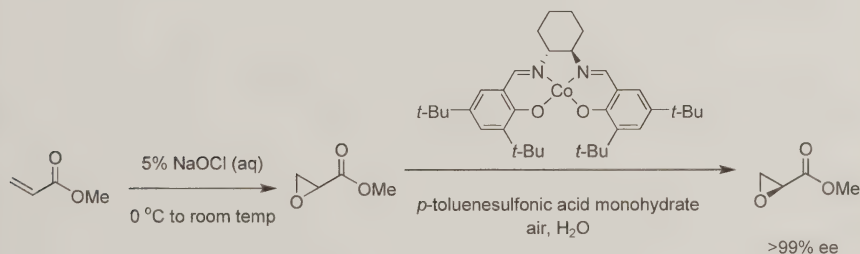
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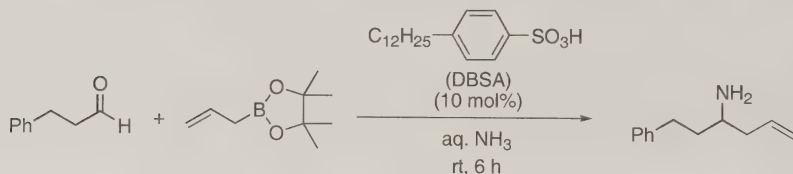
Christian P. Stevenson, Lars P. C. Nielsen, and Eric N. Jacobsen



ALLYLBORONATION OF IMINES: 1-PHENYLHEX-5-EN-3-AMINE

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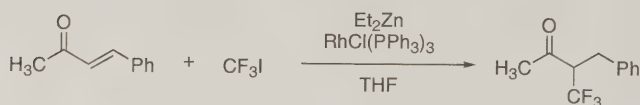
Masaharu Sugiura, Keiichi Hirano, and Shū Kobayashi



TRIFLUOROMETHYLATION AT THE α -POSITION OF α,β -UNSATURATED KETONES: 4-PHENYL-3-(TRIFLUOROMETHYL)BUTAN-2-ONE

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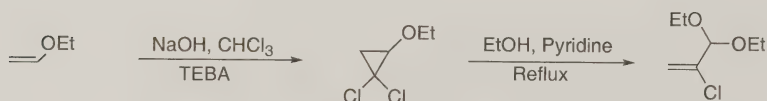
Kazuyuki Sato, Masaaki Omote, Akira Ando, and Itsumaro Kumadaki



SYNTHESIS OF 2-CHLOROACROLEIN DIETHYL ACETAL

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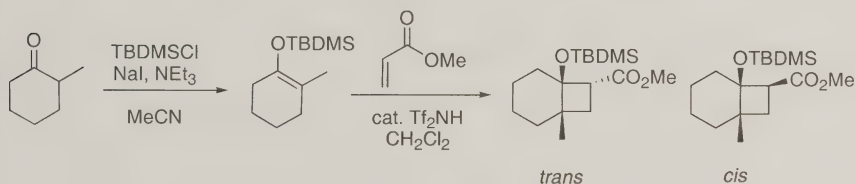
Ole H. Kvernenes and Leiv K. Sydnes



**TRIFLUOROMETHANESULFONIMIDE-CATALYZED
(2 + 2)-CYCLOADDITION OF SILYL ENOL ETHERS
WITH α,β -UNSATURATED ESTERS: 1-(*tert*-
BUTYLDIMETHYLSILOXY)-8-(METHOXYCARBONYL)-6-
METHYLBICYCLO[4.2.0]OCTANE**

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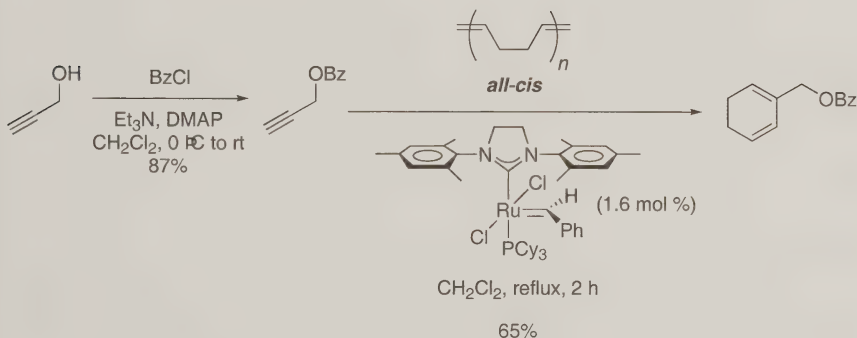
Kiyosei Takasu, Takayuki Ishii, Kazato Inanaga, and Masataka Ihara



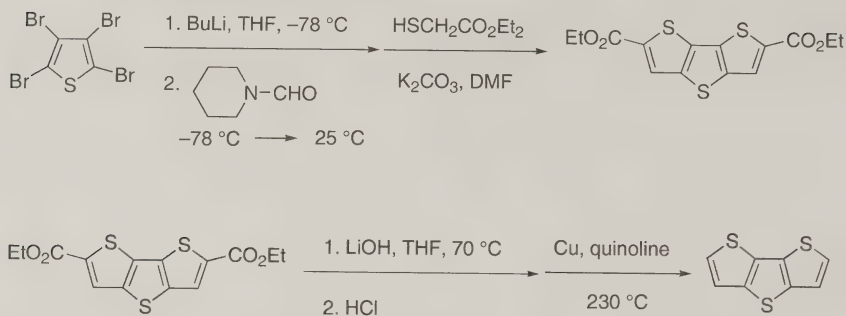
**2-SUBSTITUTED-1,3-CYCLOHEXADIENES BY
INTERMOLECULAR, METHYLENE-FREE TANDEM
ENYNE METATHESIS**

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Amol A. Kulkarni and Steven T. Diver



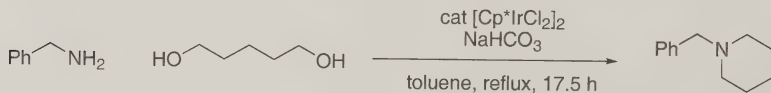
Joseph Frey, Steffen Proemmel, Michael A. Armitage, and
Andrew B. Holmes



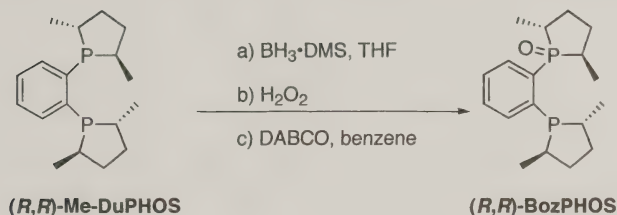
IRIDIUM-CATALYZED *N*-HETEROCYCLIZATION OF PRIMARY AMINES WITH DIOLS: *N*-BENZYLPIPERIDINE

217

Ken-ichi Fujita, Youichiro Enoki, and Ryohei Yamaguchi



PREPARATION OF ENANTIOMERICALLY PURE (*R,R*)-BozPHOS
 [(2*R*,5*R*)-1-{2-[(2*R*,5*R*)-2,5-dimethylphospholan-1-yl]phenyl}-
 2,5-dimethylphospholane 1-oxide]



Submitted by Alexandre Côté, Jean-Nicolas Desrosiers, Alessandro A. Boezio and André B. Charette.¹

Checked by Scott E. Denmark and Justin I. Montgomery.

1. Procedure

(2*R*,5*R*)-1-{2-[(2*R*,5*R*)-2,5-dimethylphospholan-1-yl]phenyl}-2,5-dimethylphospholane 1-oxide (**(*R,R*)-BozPHOS**). A flame-dried, 100-mL, one-necked, round-bottomed flask equipped with an egg-shaped magnetic stirring bar and a rubber septum is charged with (**(*R,R*)-Me-DuPHOS** (1 g, 3.26 mmol) (Note 1) in a glove-box under argon. Anhydrous THF (32 mL) (Note 2) is added to the flask via a syringe under argon and the resulting colorless solution is cooled in a 0 °C ice bath for 15 min before BH₃•DMS 10 M (360 µL, 3.6 mmol) (Note 3) is added dropwise (Note 4) via a syringe. The colorless mixture is stirred for 45 min under argon at 0 °C and H₂O₂ 35% wt. (3 x 1.15 mL, 39.2 mmol) (Note 5) is added dropwise via syringe (Note 6) at 0 °C under argon in three portions with an interval of 30 min between each addition. The mixture is stirred for an additional 45 min at room temperature, and the reaction is quenched by the dropwise addition via cannula of a saturated aqueous solution of Na₂SO₃ (40 mL) at 0 °C over 30 min (Note 7). The mixture is transferred to a 250-mL separatory funnel and the aqueous layer is extracted with ethyl acetate (3 x 100 mL), and the combined extracts are dried over Na₂SO₄ (50 g), filtered and concentrated by rotary evaporation (30 °C, 50 mmHg) to afford a white foam (1.115 g) (Note 8). The crude product and DABCO (550 mg, 4.9 mmol) (Note 9) are placed in a 100-mL, one-necked, round-bottomed flask equipped with an egg-shaped magnetic stirring bar and a rubber septum. The flask is purged under argon, then anhydrous benzene (32 mL) (Note 10) is added. The colorless

reaction mixture is stirred for 5 h in a 50 °C oil bath and then the solvent is removed by rotary evaporation (25 °C, 40 mmHg) to afford a white residue. The crude product is purified on silica gel (Notes 11, 12) to afford 977 mg (93% yield, >99% ee) of the title compound as a white solid (Notes 13 and 14).

2. Notes

1. (*R,R*)-Me-DuPHOS was purchased from Strem Chemicals, Inc. Although, it could be briefly manipulated under moisture and oxygen, it was stored under argon atmosphere in a glove-box to prevent any undesired oxidation. It was used without any prior purification.

2. Anhydrous THF was obtained by filtration through a drying column on a GlassContour system (Irvine, CA).

3. Borane•dimethyl sulfide (BH₃•DMS) was purchased from Aldrich Chemical Company, Inc. and was used without prior purification.

4. The addition lasted 1 minute.

5. H₂O₂ 35% wt. was purchased from Aldrich Chemical Company, Inc. and was used without prior purification.

6. One minute was needed for each addition.

7. The reaction is exothermic and a gas is evolved.

8. The crude product can be stored overnight under argon in a -20 °C freezer with no degradation.

9. DABCO was purchased from Aldrich Chemical Company, Inc. and was recrystallized from a 1:1 mixture of MeOH and hexanes.

10. Anhydrous benzene was obtained by filtration through a drying column on a GlassContour system (Irvine, CA).

11. The product was dissolved in dichloromethane (2 mL) and charged on a column (3 x 15 cm) of 60 g of UltraPure silica gel (40–63 µm) purchased from Silicycle. The product was eluted with 600 mL of 5% MeOH in EtOAc and collected with 8 mL fractions. The desired product was obtained in fractions 16–30, which were combined and concentrated by rotary evaporation (30 °C, 30–50 mmHg). The desired product can be visualized on TLC with a UV lamp or by developing with a KMnO₄ solution.

12. No over-oxidation occurred during the chromatography, but the pure compound is typically stored under argon.

13. The physical properties are as follows: *R_f* 0.33 (5% MeOH in EtOAc) mp 125–127 °C; HRMS (ESI⁺) *m/z* calc. for C₁₈H₂₉P₂O [M⁺ + 1]:

323.1694, found: 323.1688; Elemental Analysis calc. for $C_{18}H_{28}P_2O$: C, 67.07; H, 8.75, found: C, 67.13; H, 9.00; IR (neat) cm^{-1} 730, 738, 758, 1116, 1130, 1159, 1253, 1374, 1455, 2860, 2925; 1H NMR (400 MHz, C_6D_6) δ : 0.85 (dd, $J = 17.3, 7.4$ Hz, 3 H), 0.91–1.03 (m, 1 H), 1.06 (dd, $J = 9.1, 7.1$ Hz, 3 H), 1.26–1.37 (m, 2 H), 1.28 (dd, $J = 17.6, 8.3$ Hz, 3 H), 1.30 (dd, $J = 13.7, 6.9$ Hz, 3 H), 1.64–1.76 (m, 2 H), 1.84–2.06 (m, 4 H), 2.41–2.52 (m, 1 H), 2.58–2.71 (m, 1 H), 2.71–2.83 (m, 1 H), 7.05 (tddd, $J = 7.5, 2.6, 1.3, 0.5$ Hz, 1 H), 7.13 (tt, $J = 7.4, 1.5$ Hz, 1 H), 7.27–7.34 (m, 1 H), 7.45–7.50 (m, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ : 13.1 (dd, $J_{C-P} = 2.9, <1$ Hz), 17.5 (d, $J_{C-P} = 8.8$ Hz), 18.6 (d, $J_{C-P} = 3.9$ Hz), 20.6 (d, $J_{C-P} = 36.1$ Hz), 31.7 (dd, $J_{C-P} = 67.9, <1$ Hz), 31.8 (d, $J_{C-P} = 9.8$ Hz), 32.2 (dd, $J_{C-P} = 8.8, 1.9$ Hz), 34.4 (d, $J_{C-P} = 11.7$ Hz), 35.0 (d, $J_{C-P} = 13.6$ Hz), 36.5 (d, $J_{C-P} = 6.8$ Hz), 36.8 (dd, $J_{C-P} = 66.9, 4.9$ Hz), 36.9 (d, $J_{C-P} = 2.0$ Hz), 128.5 (d, $J_{C-P} = 10.8$ Hz), 130.9 (dd, $J_{C-P} = 2.9, <1$ Hz), 131.5 (dd, $J_{C-P} = 11.2, 9.3$ Hz), 134.2 (dd, $J_{C-P} = 10.7, 2.9$ Hz), 140.3 (dd, $J_{C-P} = 82.0, 33.2$ Hz), 144.0 (dd, $J_{C-P} = 37.1, 9.3$ Hz); ^{31}P NMR (202 MHz, C_6D_6) δ : 8.99 (d, $J = 4.6$ Hz), 62.05 (d, $J = 4.6$ Hz); $[\alpha]_D^{20} -221.6$ ($c = 0.836$, EtOH). The enantiomeric excess of the product is determined by HPLC analysis at 254 nm [Chiralpak AD, 95:5 hexanes: *i*-PrOH, 1mL/min: (R,R) t_r (major) = 7.3 min, (S,S) t_r (minor) = 10.1 min)] or determined by SFC analysis [Chiralpak AD, 20% *i*-PrOH, 150 bar CO_2 , 1 mL/min, 65° C].

14. The checkers found that the appearance of the NMR spectra was highly concentration dependent. The spectra reported were taken as follows: 1H NMR, 4 mg/1.0 mL; ^{13}C NMR, 309 mg/1.5 mL.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

The hemilabile ligand **BozPHOS** is useful for the copper-catalyzed asymmetric addition of diorganozinc reagents to *N*-diphenylphosphinoylimines.²⁻⁵ This bis-phosphine monoxide ligand can be prepared from both enantiomers of the commercially available **Me-DuPHOS** by mono-oxidation. Various methods have been reported to oxidize bidentate phosphines.⁶ Among them, Grushin’s method involving palladium acetate⁷

was unsuitable because it afforded a mixture of the unreacted bis-phosphine, its mono-oxide (40%), its bis-oxide and an unidentified phosphonium salt. The procedure described above employs a selective mono-protection of the bis-phosphine with $\text{BH}_3 \cdot \text{DMS}$ followed by a mono-oxidation with H_2O_2 . During this process, no bis-oxidation is obtained even if an excess of H_2O_2 is used. Traces of unreacted **Me-DuPHOS** can be separated easily by silica gel flash chromatography since **BozPHOS** is air stable. The procedure described above can be accomplished on a 0.5 to 10 g-scale to obtain **BozPHOS** in an 87 to 93% yield.

1. Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal (Québec) Canada, H3C 3J7.
2. Desrosiers, J.-N.; Côté, A.; Boezio, A. A.; Charette, A. B. *Subsequent procedure in this volume*, **2004**.
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4. Côté, A.; Boezio, A. A.; Charette, A. B. *Angew. Chem. Int. Ed.* **2004**, *43*, 6525–6528.
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7. Grushin, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5831–5832.

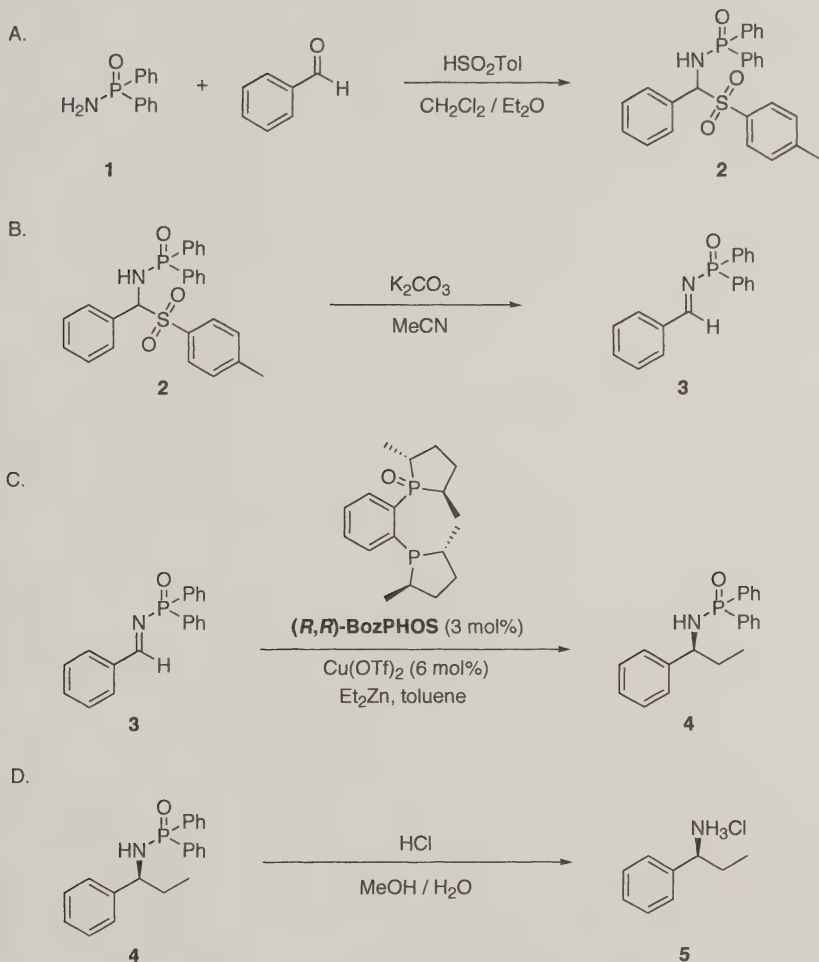
Appendix

Chemical Abstracts Nomenclature; (Registry Number)

(*R,R*)-Me-DuPHOS: Phospholane 1,1'-(1,2-phenylene)bis[2,5-dimethyl-,
[2*R*-[1(2'*R**,5'*R**),2a,5b]]-; (147253-67-6)
DABCO: 1,4-Diazabicyclo[2.2.2]octane; (280-57-9)
(*R,R*)-BozPHOS: Phospholane, 1-[2-[(2*R*,5*R*)-2,5-dimethyl-1-oxido-1-
phospholanyl]phenyl]-2,5-dimethyl-, (2*R*,5*R*)-; (38132-66-8)

PREPARATION OF ENANTIOMERICALLY ENRICHED (1*S*)-1-PHENYLPROPAN-1-AMINE HYDROCHLORIDE BY A CATALYTIC ADDITION OF DIORGANOZINC REAGENTS TO IMINES

[Benzenemethanamine, α -ethyl-, hydrochloride, (α *S*)-]



Submitted by Jean-Nicolas Desrosiers, Alexandre Côté, Alessandro A. Boezio and André B. Charette.¹

Checked by Scott E. Denmark and Justin I. Montgomery.

1. Procedure

A. *N*-[(4-Methylphenyl)sulfonyl(phenyl)methyl]-*P,P*-diphenylphosphinic amide (**2**). A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer (fitted with a 7-cm Teflon paddle) and two rubber septa is charged with **1** (9.55 g, 43.97 mmol) (Notes 1, 2). Dichloromethane (75 mL) (Note 3) and diethyl ether (365 mL) (Note 4) are added successively to the flask. The resulting suspension is stirred for 5 min and benzaldehyde (6.7 mL, 65.96 mmol) (Note 5) is added via a syringe. *p*-Toluenesulfinic acid (10.3 g, 65.96 mmol) (Note 6) is then added in one portion at room temperature. The reaction mixture is capped and allowed to stir for 48 h (200 rpm), during which time a white precipitate is slowly formed. The mixture is filtered through a sintered glass funnel and the white solid is washed with diethyl ether (100 mL) and dried under vacuum (25 °C, 0.1 mmHg) to afford 18.12–18.45 g (89–91% yield) (Note 7) of the title compound.

B. *N*-[(Phenyl)methylene]-*P,P*-diphenylphosphinic amide (**3**). A flame-dried 1-L, one-necked, round-bottomed flask equipped with an egg-shaped magnetic stirring bar and a rubber septum is charged with **2** (18.00 g, 39.00 mmol) and anhydrous potassium carbonate (26.95 g, 195.0 mmol) (Note 8). The flask is purged with argon and anhydrous acetonitrile (365 mL) (Note 9) is added via cannula under argon at room temperature. The resulting suspension is vigorously stirred under argon at room temperature for 12 h. The reaction mixture is filtered through a sintered glass funnel and the residue is washed with acetonitrile (50 mL). The filtrate is concentrated at 30 °C by rotary evaporation (30–50 mmHg) to afford 10.88 g (91% yield) (Note 10) of the title compound as an off-white solid.

C. *N*-[(1*S*)-1-Phenylpropyl]-*P,P*-diphenylphosphinic amide (**4**). A flame-dried, 500-mL, one-necked, round-bottomed flask equipped with an egg-shaped magnetic stirring bar and a rubber septum is charged with Cu(OTf)₂ (745 mg, 2.06 mmol) (Note 11) and (*R,R*)-**BozPHOS** (332 mg, 1.03 mmol) (Note 12) in a glove-box under argon. Anhydrous toluene (172 mL) (Note 13) is added to the flask at room temperature via cannula. The resulting dark green heterogeneous solution is stirred for 1 h at room temperature and neat diethylzinc (7.05 mL, 68.78 mmol) (Note 14) is added at room temperature under argon via a 10-mL gas-tight syringe (**CAUTION: NEAT DIETHYLZINC IS HIGHLY PYROPHORIC**). The resulting dark brown suspension is stirred for 20 min at room temperature and then is

diluted by the addition of anhydrous toluene (172 mL) via cannula under argon. The mixture is cooled to 0 °C (internal temperature measured with a thermocouple probe (Note 15)) with a cryostat (Note 16) and the system is opened to add the solid **3** (10.50 g, 34.39 mmol) quickly in one portion. The flask is sealed with a septum and purged with argon over a period of 5 min. The reaction mixture is allowed to stir for 21 h at 0 °C under argon. Aqueous saturated ammonium chloride (100 mL) is added dropwise via cannula at 0 °C to quench the reaction. The mixture is poured into a 2-L separatory funnel containing aqueous saturated ammonium chloride (400 mL). The biphasic mixture is extracted with dichloromethane (3 x 500 mL). The combined extracts are dried over Na₂SO₄ (150 g), filtered and concentrated at 40 °C by rotary evaporation (100–150 mmHg) and then at 20 mmHg to afford 11.82 g of an off-white solid containing the title compound and the catalyst. This mixture is used without purification for the next step. A 200.0 mg sample of the crude product is purified by silica gel chromatography (Note 17) to afford 185.7 mg (92.9% recovery, 97% ee) (Note 18) of the title compound as a white solid.

D. *(1S)-1-Phenylpropan-1-amine hydrochloride (5)*. A 1-L, one-necked, round-bottomed flask equipped with an egg-shaped magnetic stirring bar is charged with **4** (11.62 g, 92.9% purity, 32.19 mmol). A mixture of methanol (270 mL) (Note 19) and concentrated aqueous HCl (60.9 mL) (Note 21) is added to the flask. The flask is capped and the resulting clear, bright yellow solution is allowed to stir at room temperature for 16.5 h (Note 20). The reaction mixture is then concentrated at 40 °C by rotary evaporation (10 mmHg) and the residue is dissolved in 1.21 M aqueous HCl (300 mL). The precipitate (Note 22) is removed by filtration on a sintered-glass funnel. The acidic filtrate is extracted with diethyl ether (3 x 300 mL) (Note 23), then it is basified (pH ≥ 12, Note 24) by adding 2 M NaOH (~300 mL). The resulting milky solution is extracted with dichloromethane (4 x 300 mL). The combined extracts are dried over Na₂SO₄ (160 g) and filtered. A solution of HCl in diethyl ether (1 M, 67.6 mL, 67.6 mmol) (Note 25) is added to the organic layer and the mixture is concentrated at 30 °C by rotary evaporation (200–250 mmHg), then at 50–100 mmHg. The resulting off-white to yellow solid (5.60 g) is triturated with ethyl acetate (50 mL) and filtered to afford 4.89 g (88% yield, 97% ee) (Notes 26–28) of the pure title compound as a white solid.

2. Notes

1. *P,P*-Diphenylphosphinic amide (**1**) was purchased from Alfa Aesar as diphenylphosphinamide (98+%).

2. *P,P*-Diphenylphosphinic amide (**1**) can be prepared by the following procedure (not attempted by the checkers): A flame-dried 2-L, one-necked, round-bottomed flask, equipped with an egg-shaped magnetic stirring bar, a rubber septum and an internal thermocouple probe is purged with argon. The flask is then charged with 1 L of anhydrous dichloromethane under argon. The septum is removed and acetone oxime (16.56 g, 227 mmol) is added quickly in one portion and the flask is sealed and purged again with argon. Freshly distilled triethylamine (31.6 mL, 227 mmol) is added via a syringe and the resulting colorless solution is cooled to $-78\text{ }^{\circ}\text{C}$ (internal temperature) with an acetone/dry ice bath (approximately 30 min are needed to reach this temperature). Freshly distilled, colorless chlorodiphenylphosphine (42 mL, 227 mmol) is added dropwise (2 mL/min) via a syringe at such a rate that the internal temperature does not exceed $-70\text{ }^{\circ}\text{C}$. After the addition is complete, the resulting milky solution is stirred 15 min at $-78\text{ }^{\circ}\text{C}$ under argon. The cooling bath is removed, and the solution is allowed to warm to room temperature over a period of 1.5 h and stirred 1 h at that temperature. The milky solution becomes clear. The solvent is removed under reduced pressure and the resulting off-white to yellow solid is dried under vacuum for 12 h. The residue is dissolved in acetone (200 mL) and dried under reduced pressure. This last step is repeated once again. (This step makes the removal of the solid from the flask easier. Furthermore, the solid can be ground to a finer powder, which facilitates the next step. This step can be avoided but problems may occur, such as the formation of a gummy yellow solid during the addition to the aqueous ammonium hydroxide solution. This problem can be related to the presence of dichloromethane in the solid. Heating the mixture with a heat gun to dissolve everything can solve this problem, but lower yields and side-products are obtained.) The solid is removed from the flask and ground to a powder using a mortar and pestle. The powder is added in one portion into an Erlenmeyer flask containing a stirring solution (magnetic stirring bar) of concentrated aqueous ammonium hydroxide (660 mL) and distilled water (330 mL). The mixture is usually heterogeneous and the precipitate is a white solid. Sometimes the solid added dissolves rapidly to form a clear yellow solution and, after few seconds, a white solid starts to precipitate. The heterogeneous mixture is stirred for 45 min and **1** is obtained as a white solid by filtration

through a sintered glass funnel. The aqueous filtrate is extracted with dichloromethane (3 x 600 mL). The combined extracts are dried over Na₂SO₄, filtered and evaporated under reduced pressure. The white solid obtained is combined with the white precipitate obtained above after filtration. The combined solids are dissolved in benzene (300 mL) and evaporated. This step is repeated three times to remove traces of water to afford 46.31–47.87 g (94–97% yield) of **1**. The purity can be increased by crystallization in ethyl acetate.

3. Dichloromethane (ACS grade) was purchased from Fisher Scientific and was used as received.

4. Diethyl ether (ACS grade) was purchased from Fisher Scientific and was used as received.

5. Benzaldehyde was purchased from Aldrich Chemical Company, Inc. and was freshly distilled (70–72 °C, 20 mmHg) prior to use.

6. *p*-Toluenesulfinic acid was prepared according to the procedure described in *Organic Syntheses*, see ref 2.

7. The physical properties are as follows: mp 153–155 °C (sealed tube); IR (neat) cm⁻¹: 725, 748, 756, 888, 1030, 1086, 1109, 1124, 1148, 1191, 1289, 1301, 1312, 1436, 1459, 1597, 2954, 3056, 3205; ³¹P NMR (202 MHz, DMSO) δ: 24.98. Due to the very low solubility of the compound in DMSO, clean NMR spectral data are difficult to obtain because minor impurities are much more soluble than the compound of interest.

8. Granular potassium carbonate was purchased from Aldrich Chemical Company, Inc. and was ground to a powder using a mortar and pestle then dried under vacuum (100 °C, 1 mmHg).

9. Anhydrous acetonitrile was obtained by filtration through a drying column on a GlassContour system (Irvine, CA).

10. The purity is greater than 97% according to the ³¹P and ¹H NMR spectra and the only observed impurities are benzaldehyde and **1**. These impurities can be removed on a short pad of silica gel (EtOAc 100%). The physical properties of the purified material are as follows: mp 144–146 °C; R_f 0.47 (EtOAc); MS (ESI+) *m/z* 307.1 (20%), 306.1 (M⁺+H, 100%), 233.1 (37%), 219.1 (22%), 201.2 (14%); Anal. calcd for C₁₉H₁₆NOP: C, 74.74; H, 5.28; N, 4.59. found: C, 74.45; H, 5.27; N, 4.71; IR (KBr) cm⁻¹: 704, 729, 752, 832, 848, 926, 998, 1074, 1110, 1127, 1199, 1311, 1368, 1443, 1577, 1597, 1626, 1663, 1698, 2881, 3024, 3056; ¹H NMR (400 MHz, CDCl₃) δ: 7.39–7.56 (m, 9 H), 7.90–8.02 (m, 6 H), 9.32 (d, *J* = 32.2 Hz, 1 H); ¹³C NMR (100 MHz, CHCl₃) δ: 128.3 (d, *J*_{C-P} = 12.5 Hz), 128.8, 130.0, 131.4 (d, *J*_{C-P} = 9.2 Hz), 131.7 (d, *J*_{C-P} = 3.6 Hz), 132.8 (d, *J*_{C-P} = 127.5 Hz), 133.5,

135.6 (d, $J_{C-P} = 24.2$ Hz), 173.5 (dd, $J_{C-P} = 7.7, 3.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ : 24.78.

11. $\text{Cu}(\text{OTf})_2$ was purchased from Strem Chemicals, Inc. It was stored under argon atmosphere in a glove-box and was used without prior purification.

12. (*R,R*)-BozPHOS was prepared according to the preceeding procedure and was stored under argon in a glove box.

13. Anhydrous toluene was obtained by filtration through a drying column on a GlassContour system (Irvine, CA).

14. Diethylzinc is a moisture sensitive and pyrophoric liquid and must be manipulated in an inert atmosphere. Neat diethylzinc was purchased from Aldrich Chemical Co. Inc. and was used without prior purification.

15. A PFA coated thermocouple probe, Type K (Omega Engineering, Inc.) was inserted through the septum after the addition of diethylzinc to monitor the internal temperature of the reaction solution.

16. Approximately 35 min are needed to reach that temperature. A Neslab, model CC-65II, cryostat was used to maintain the reaction mixture at 0 °C.

17. The mixture was dissolved in a minimum amount of dichloromethane and then was charged onto a column (diameter = 2 cm, height = 15 cm) of 200 g of UltraPure silica gel (40–63 μm) purchased from Silicycle. The column was eluted with EtOAc and 8-mL fractions were collected. Fractions 15-33 were combined and concentrated by rotary evaporation (30 °C, 50 mmHg). The desired product can be visualized on TLC with a UV lamp or by spraying with a phosphomolybdic acid solution. The R_f value of the title compound in EtOAc is 0.37.

18. The physical properties are as follows: mp 127–129 °C; MS (ESI+) m/z : 337.2 ($\text{M}^+ + \text{H}$, 21%), 336.1 (M^+ , 100%), 233.2 (17%), 219.2 (18%), 218.1 (28%), 201.2 (9%). Anal. calcd. for $\text{C}_{21}\text{H}_{22}\text{NOP}$: C, 75.21; H, 6.61; N, 4.18; found: C, 74.90; H, 6.55; N, 4.35; IR (KBr) cm^{-1} : 722, 752, 904, 933, 1057, 1090, 1109, 1122, 1182, 1198, 1438, 1460, 2873, 2926, 2963, 3055, 3135; ^1H NMR (500 MHz, CDCl_3) δ : 0.78 (t, $J = 7.5$ Hz, 3 H), 1.78–1.88 (m, 1 H), 1.96–2.06 (m, 1 H, exchanges with D_2O), 3.27 (br, 1 H), 4.09 (pent, $J = 8.4$ Hz, 1 H), 7.14–7.16 (m, 2 H), 7.21–7.34 (m, 5 H), 7.39–7.50 (m, 4 H), 7.75 (ddt, $J = 12.0, 6.9, 1.5$ Hz, 2 H), 7.86 (ddt, $J = 12.0, 7.1, 1.3$ Hz, 2 H); ^{13}C NMR (126 MHz, CHCl_3) δ : 10.5, 32.5 (d, $J_{C-P} = 3.9$ Hz), 57.1, 126.5, 127.1, 128.3 (d, $J_{C-P} = 12.9$ Hz), 128.4, 128.4 (d, $J_{C-P} = 12.9$ Hz), 131.7 (d, $J_{C-P} = 2.7$ Hz), 131.8 (d, $J_{C-P} = 9.2$ Hz), 131.8 (d, $J_{C-P} = 2.8$ Hz), 131.9 (d, $J_{C-P} = 131.0$ Hz), 132.6 (d, $J_{C-P} = 10.2$ Hz), 133.2 (d, $J_{C-P} =$

128.0 Hz), 143.5 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR (202 MHz, CDCl_3) δ : 22.74; $[\alpha]_{\text{D}}^{20}$ -41.6 (c = 2.14, MeOH). The enantiomeric excess of the product is determined by HPLC analysis at 254 nm [Chiralpak, AD, 85:15 hexanes: *i*-PrOH, 1mL/min: (*R*) t_{r} (minor) = 10.2 min, (*S*) t_{r} (major) = 13.4 min)].

19. Methanol (ACS grade) was purchased from Fisher Scientific and was used as received.

20. The reaction was followed by ^{31}P NMR spectroscopic analysis. The rate of disappearance of the signal at 23.2 ppm is proportional to the rate of formation of the desired product. The new signals at 34.3 ppm and at 36.6 ppm correspond, respectively, to diphenylphosphinic acid and methyl diphenylphosphinate.

21. Aqueous concentrated HCl (ACS grade) was purchased from Fisher Scientific and was used as received.

22. The precipitate is diphenylphosphinic acid.

23. This step is used to extract the methyl diphenylphosphinate.

24. An ColorpHast indicator strip purchased from EM Science, Inc. was used to measure the pH.

25. 1 M Hydrogen chloride solution in diethyl ether was purchased from Aldrich Chemical Company, Inc. and was used as received.

26. The physical properties are as follows: mp 231–234 °C; MS (EI) m/z : 135.1, (4%), 106.1 (100%), 79.1 (18%), 74.1 (75%), 59.0, (100%). Anal. calcd. for $\text{C}_9\text{H}_{14}\text{ClN}$: C, 62.97; H, 8.22; N, 8.16; found: C, 62.71; H, 8.33; N, 8.18; IR (KBr) cm^{-1} : 754, 764, 1386, 1394, 1458, 1509, 1600, 2536, 2618, 2685, 2914, 2963, 3035; ^1H NMR (400 MHz, MeOD) δ : 0.88 (t, J = 7.3 Hz, 3 H), 1.90–2.10 (m, 2 H), 4.15 (dd, J = 9.5, 5.8 Hz, 1 H), 7.39–7.49 (m, 5 H); ^{13}C NMR (100 MHz, MeOD) δ : 10.5, 28.7, 58.3, 128.4, 130.3, 130.3, 138.1; $[\alpha]_{\text{D}}^{20}$ +16.2 (c = 1.03, MeOH).

27. The enantiomeric excess of the product was determined on the trifluoroacetyl derivative of the amine by GC analysis with an FID detector (Astec ChiralDEX GT-A (30 m x 0.32 mm) 10 psi, 90 °C isothermal): (*R*) t_{r} (minor) = 19.59 min, (*S*) t_{r} (major) = 20.53 min). To prepare the trifluoroacetamide derivative, 1 mL of 2 M aqueous NaOH solution was added to 10 mg of the amine hydrochloride salt in a 5 mL conical vial. The aqueous layer was extracted with 1 mL of dichloromethane. The organic layer was dried over Na_2SO_4 (0.5 g), and was decanted into a 5-mL round-bottomed flask. An egg-shaped magnetic stir bar and 250 μL of trifluoroacetic anhydride were added and the mixture was stirred at room temperature under argon for 5 min. The solvent and excess reagents were removed by rotary evaporation (80 mmHg, 25 °C, 5 min; then 5 mmHg, 25

°C, 10 min). The solid residue was dissolved in 1 mL of dichloromethane and the liquid was filtered through a syringe filter for GC analysis. For the enantioenriched compounds, the sample was concentrated to ca. 0.1 mL to observe the minor isomer.

28. The submitters were able to determine the enantiomeric excess of the free amine directly by GC analysis with an FID detector [Beta DexTM 120; 30 °C to 85 °C in 11 min and isothermal thereafter: (*R*) *t_r* (minor) = 43.0 min, (*S*) *t_r* (major) = 43.6 min)].

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.




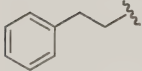



3. Discussion

This procedure provides an attractive route to α -substituted chiral amines by using a catalytic asymmetric addition of a diorganozinc reagent. Numerous activating groups have been reported for the catalytic asymmetric additions of diorganozinc reagents to imines. Among them, *N*-tosylimines,⁴ *N*-arylimines⁵ and *N*-acylimines⁶ have been used as precursors. Herein, we use the *N*-phosphinoyl group because of its facile cleavage under mildly acidic conditions. The other activating groups require harsh oxidizing, reducing or basic conditions for cleavage. Another advantage of using the *N*-phosphinoyl activating group is that a crystalline product is generally obtained. This product can often be recrystallized from low polarity solvents to increase enantiopurity.⁷

Earlier syntheses of *N*-diphenylphosphinoylimines involved either a condensation between an aldehyde and *N*-diphenylphosphinoyl amide promoted by TiCl₄ and Et₃N⁸ or a radical rearrangement between an oxime and chlorodiphenylphosphine with the presence of Et₃N.⁹ These methods are not useful for the synthesis of *N*-phosphinoylimines on large scale because of the low yields that result from tedious workup procedures or extensive purification. However, the present synthesis of *N*-phosphinoylimines via a stable sulfinyl adduct is very effective for production of multi-gram quantities of material.¹⁰ The procedure, which consists of deprotonating the sulfinyl adduct **2** with K₂CO₃ to induce imine formation, is general, straightforward, inexpensive, and high yielding.

Several *N*-phosphinoylimines derived from aromatic or aliphatic aldehydes can be generated by this sequence. For instance, acetaldehyde, heptanal, isovaleraldehyde, hydrocinnamaldehyde, isobutyraldehyde, cyclopentanecarboxaldehyde and cyclohexanecarboxaldehyde afford the desired sulfinic acid adducts of the *N*-phosphinoylimine on a small scale (Table 1).¹¹ These adducts are generated in diethyl ether and precipitate from the reaction mixture as white solids. In the present case, a mixture of dichloromethane and diethyl ether gives a better yield and a higher purity of the sulfinyl adduct **2**. Because of the higher solubility of its adduct, 1-naphthaldehyde gives a poor yield (30%). To avoid problems of handling unstable imines of aliphatic aldehydes, it is also possible to carry out the asymmetric addition directly on the sulfinic acid adduct.^{11,12} The same reaction conditions are used except that an excess of diethylzinc (2.5 equiv) is needed to generate the imine *in situ*.

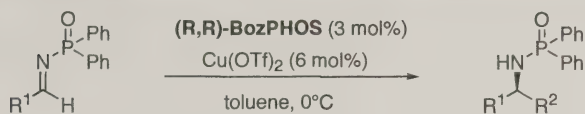
Table 1. Sulfinyl adducts synthesis^{a,b}

$ \begin{array}{ccc} \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{H} \\ (1.5 \text{ equiv}) \end{array} & \xrightarrow[\text{Et}_2\text{O, r.t., 20 hr}]{\begin{array}{c} \text{H}_2\text{N}-\text{P}(\text{Ph})_2 \text{ (1 equiv)} \\ \text{HSO}_2\text{Tol (1.5 equiv)} \end{array}} & \begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{CH}-\text{P}(\text{Ph})_2 \\ \\ \text{SO}_2\text{Tol} \end{array} \end{array} $		
Entry	R	Yield (%)
1		91
2		87
3		84
4 ^c		97
5		88
6		95
7		72

^a See reference 11 ^b 5 mmol scale ^c 10 mmol scale.

The copper-catalyzed addition of diorganozinc reagents to alkyl- or aryl-substituted *N*-phosphinoylimines proceeds in high yields, with excellent enantioselectivities and without using a large excess of organometallic reagents. Furthermore, both enantiomers of the BozPHOS ligand synthesized from the commercially available enantiomers of Me-DuPHOS. The reaction proceeds well with different dialkyl- (Me_2Zn , *n*- Bu_2Zn and *i*- Pr_2Zn) or functionalized zinc reagents (Table 2).⁷ This system can also tolerate a wide variety of *N*-phosphinoylimines obtained from either electron-poor or electron-rich aldehydes.^{7, 13}

Table 2. Enantioselective Addition of Dialkylzinc Reagents to Imines^{a,b}



Entry	R^1	R^2_2Zn	Yield (%)	ee (%)
1		Et_2Zn	97	99
2		Et_2Zn	96	97
3		Et_2Zn	94	98
4		Et_2Zn	91	98
5		Et_2Zn	97	97
6		Et_2Zn	95	94
7 ^c		Et_2Zn	97	96
8 ^d		Me_2Zn	87	97
9		nBu_2Zn	92	96
10 ^e		iPr_2Zn	84	95

^a See reference 7 ^b 2 mmol scale ^c Specific conditions: 2.8 mol% $Cu(OTf)_2$ / 3.0 mol% (R,R) -BozPHOS at $-15^\circ C$ ^d Specific conditions: 5.0 mol% $Cu(OTf)_2$ / Toluene / 5.0 mol% (R,R) -BozPHOS at r.t. ^e 3 equiv of iPr_2Zn .

1. Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal (Québec) Canada, H3C 3J7.
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

P,P-Diphenylphosphinic amide; (5994-87-6)

Benzaldehyde; (100-52-7)

p-Toluenesulfinic acid: Benzenesulfinic acid, 4-methyl-; (536-57-2)

N-[(4-Methylphenyl)sulfonyl(phenyl)methyl] *P,P*-diphenylphosphinic amide; (701291-86-3)

N-[(Phenyl)methylene]-*P,P*-diphenylphosphinic amide: Phosphinic amide, *P,P*-diphenyl-*N*-(phenylmethylene)-; (67764-52-7)

Cu(OTf)₂: Methanesulfonic acid, trifluoro-, copper(2+) salt; (34946-82-2)

(*R,R*)-BozPHOS: Phospholane, 1-[2-[(2*R*,5*R*)-2,5-dimethyl-1-oxido-1-

phospholanyl]phenyl]-2,5-dimethyl-, (2*R*,5*R*)-; (38132-66-8)

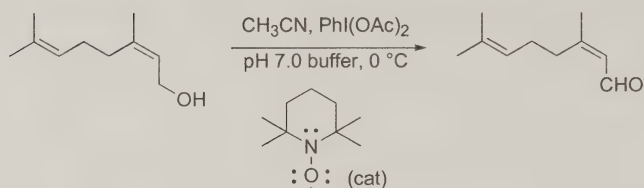
Diethylzinc; (557-20-0)

N-[(1*S*)-1-Phenylpropyl]-*P,P*-diphenylphosphinic amide: Phosphinic amide,

P,P-diphenyl-*N*-[(1*S*)-1-phenylpropyl]-; (106651-15-4)

(1*S*)-1-Phenylpropan-1-amine hydrochloride: Benzenemethanamine, α -ethyl-, hydrochloride, (α *S*)-: (19146-52-2)

**OXIDATION OF NEROL TO NERAL WITH IODOSOBENZENE
DIACETATE AND TEMPO**
[(Z)-3,7-Dimethyl-2,6-octadienal]



Submitted by Giovanni Piancatelli and Francesca Leonelli.^{1a}
Checked by Nga Do and John Ragan.^{1b}

1. Procedure

(Z)-3,7-Dimethyl-2,6-octadienal. A 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with the following order of the reagents: acetonitrile (28 mL) (Note 1), *(Z)*-3,7-dimethyl-2,6-octadien-1-ol (nerol) (5.70 mL, 32.5 mmol) (Note 2), aqueous pH 7.0 buffer solution (8 mL) (Note 3), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (490 mg, 3.24 mmol) (Note 4), and iodobenzene diacetate (IBD) (11.49 g, 35.71 mmol) (Note 5). The reaction mixture is stirred at 0 °C (Note 6) until nerol is no longer detectable by TLC analysis (Note 7). The reaction mixture is diluted with diethyl ether (100 mL) and transferred to a 500-mL separatory funnel. The orange mixture is washed with saturated aqueous sodium thiosulfate (2 x 50 mL) (Note 8). The aqueous phase is separated and extracted with diethyl ether (3 x 35 mL). The combined organic layers are washed with saturated aqueous sodium hydrogen carbonate (40 mL) and then with saturated aqueous sodium chloride (40 mL) (Note 9). The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator (35 °C, 70 mmHg). The residue is purified by column chromatography on silica gel (Note 10), using a 1:9 mixture of diethyl ether and hexanes as eluent (Note 11) to afford 4.30–4.39 g (87–89%) of *(Z)*-3,7-dimethyl-2,6-octadien-1-al (neral) as a colorless oil (Note 12). The material is homogenous by TLC, IR, ¹H and ¹³C-NMR (Note 13).

2. Notes

1. “RPE-For analysis”-grade CH_3CN , as supplied by Carlo Erba Reagents (Italy), was used.

2. Nerol (97%) was purchased from Aldrich and used directly without purification. The compound revealed traces of geraniol (< 3%) from GCMS analysis (Shimadzu GCMS-QP5000; EQUITYTM-5 FUSED SILICA Capillary Column 30 m x 0.32 mm x 0.25 μm film thickness; 80 °C (1 min), 80-240 °C (16 min), 240 °C (1 min)); $t_{\text{nerol}} = 8.43$, $t_{\text{rgeraniol}} = 8.75$. The checkers used an Agilent HP-5 fused silica capillary column, 30 m x 0.32 mm x 0.25 μm ; 250 °C detector, 100 °C isothermal program at 2 mL/min. This system gave the following retention times: $t_{\text{nerol}} = 7.3$ min, $t_{\text{neral}} = 7.8$ min, $t_{\text{geraniol}} = 8.4$ min, $t_{\text{geranial}} = 9.1$ min. The checkers’ lot of nerol (also purchased from Aldrich) showed <0.5% geraniol contamination.

3. The pH 7.0 buffer solution was purchased from Fluka.

4. TEMPO (98%) was purchased from Aldrich and used as received.

5. IBD (98%) was purchased from Aldrich and used as received.

6. An ice-bath is placed under the reaction flask after the dissolution of IBD (≈ 3 min) because the reaction is slightly exothermic. On a smaller scale (1-5 mmol) this precaution is not necessary. The checkers placed the reaction flask in an ice bath prior to addition of the TEMPO and IBD; as the IBD began dissolving, an internal temperature probe showed a temperature rise of 6–9 °C over the course of the reaction. This was not an issue on the scale run, but should be carefully monitored if the reaction were to be significantly increased in scale.

7. The oxidation reaction is usually very fast and is complete after 20 min on the scale described above. The reaction was checked by TLC to confirm completion. Thin-layer chromatography analysis was carried out on E.Merck silica gel F254 plates by elution with Et_2O /hexanes (3/7), then sprayed with 2 N H_2SO_4 solution and heated with a hot plate for 1 min. The alcohol starting material has an $R_f = 0.29$ (light brown) and the aldehyde product has an $R_f = 0.66$ (deep purple). The reaction can also be monitored by GC/MS, as indicated by the checkers in Note 3.

8. Washing with saturated aqueous sodium thiosulfate removes TEMPO from the organic phase that becomes light yellow. If the organic phase should be still orange after the two washings, the solution is shaken in the separatory funnel with 50 mL of saturated aqueous sodium thiosulfate and 15 mL of 0.5 N HCl until it becomes light yellow (the checkers found this extra thiosulfate-HCl wash to be necessary). TEMPO must be removed

carefully at this stage, because it cannot be removed in the chromatographic purification.

9. The aqueous phase must be neutral. Acidic impurities can catalyze (*E*)/(*Z*) isomerization of the aldehyde in the purification stage.

10. Silica gel 60 (0.063-0.2 mm/ 70-230 mesh ASTM), purchased from Macherey-Nagel, was used. The column chromatography was performed using a 1/20 ratio between the crude product and silica gel.

11. The solvent required for the purification of the product varies from 1.4 to 1.6 L. The chromatographic solvent is removed with a rotary evaporator (35 °C, 70 mmHg).

12. The checkers used diethyl ether:hexane (2:8) for column elution. Attempted purification by distillation (bp 118–120 °C, 20 mmHg) led to significant olefin isomerization (the pot residue was a 50:50 mixture of neral and geranial).

13. The following analytical data have been obtained for (*Z*)-3,7-dimethyl-2,6-octadien-1-al: IR (CHCl₃) cm⁻¹: 1675 (C=O), 1635 (C=C); ¹H NMR (400 MHz, CDCl₃) δ: 1.58 (s, 3 H), 1.67 (s, 3 H), 1.97 (d, *J* = 1.2 Hz, 3 H), 2.15–2.25 (m, 2 H), 2.57 (t, *J* = 7.5 Hz, 2 H), 5.06–5.11 (m, 1 H), 5.86 (d, *J* = 8.3 Hz, 1 H), 9.88 (d, *J* = 8.3 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ: 17.9, 25.3, 25.9, 27.2, 32.7, 122.4, 128.8, 133.9, 164.1, 191.0; GCMS purity >97%, *t*_r=8.56. The compound revealed traces of geranial (< 3%, *t*_r=8.98) from GCMS analysis (See Note 3).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

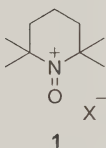
3. Discussion

The catalytic procedure described here illustrates a fast and inexpensive conversion of a (*Z*)-configured primary allylic alcohol into the corresponding (*Z*)-configured α,β-unsaturated aldehyde in high yields. The result demonstrates the chemoselectivity of the process, in that the easily isomerizable *Z*-configuration of the nerol is maintained.

Various methods for the oxidation of nerol to neral are available. Although individually having some synthetic advantages, most methods suffer from one or more experimental drawbacks, such as severe or delicate

reaction conditions, complicated reaction procedures, and the need to use toxic or unstable reagents.²

Oxammonium salts **1** are the effective oxidant species derived from TEMPO, and have been used extensively either in stoichiometric or in catalytic amounts for the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds.³ Compound **1** has been generated *in situ* from nitroxyl radicals, such as TEMPO, in combination with a number of secondary oxidants.⁴



Hypervalent iodine reagents have been used recently for a variety of organic transformations.⁴ *Inter alia*, IBD in combination with catalytic amounts of TEMPO is used as a stoichiometric oxidant in the conversion of primary and secondary alcohols to carbonyl compounds.⁵ This oxidation protocol works efficiently at room temperature in dichloromethane (and also in most common organic solvents and neat in some cases) and can be

Table 1. Oxidation of Primary Alcohols to Aldehydes⁵

Entry	Substrate	Product	Time (h)	yield (%)
1	THPO-CH=CH-CH ₂ OH	THPO-CH=CH-CHO	0.2	95
2			1	70
3	PhS-CH=CH-CH ₂ OH	PhS-CH=CH-CHO	1	70
4			15	55
5			3	95

performed in an open flask without special precautions (e.g. inert atmosphere or dry solvent). This process exhibits a very high degree of selectivity for the oxidation of primary alcohols to aldehydes, without noticeable over-oxidation to carboxyl compounds, and a high chemoselectivity in the presence of either secondary alcohols or of other oxidizable moieties.⁵

Many sensitive protective groups are not affected by this method. Some examples of carbonyl compounds synthesized with this method are reported in Table 1.⁵

1. (a) Dipartimento di Chimica, Università "La Sapienza", Piazzale Aldo Moro 5, 00185 Roma, Italy. (b) Chemical Research & Development, Pfizer Global Research & Development, Eastern Point Road, Groton, CT, USA.
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

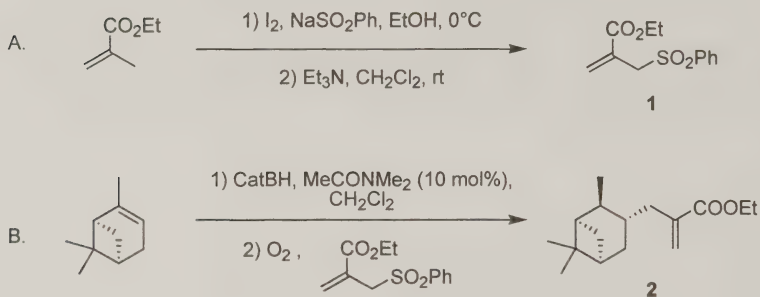
(*Z*)-3,7-Dimethyl-2,6-octadien-1-ol (nerol); (106-25-2)

2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO); 2,2,6,6-Tetramethyl-1-piperidinyloxy; (2564-83-2)

Iodobenzene diacetate (IBD): Bis(acetato- κ O)phenyliodine; (3240-34-4)

(*Z*)-3,7-Dimethyl-2,6-octadien-1-al (neral); (2*Z*)-3,7-Dimethyl-2,6-octadienal; (106-26-3)

RADICAL ALLYLATION OF *B*-ALKYLCATECHOLBORANES
[Ethyl 2-[(1*S*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)methyl]acrylate]



Submitted by Vincent Darmency, Eoin Martin Scanlan, Arnaud Pierre Schaffner and Philippe Renaud.¹

Checked by Bin Sui and Dennis P. Curran.

1. Procedure

A. *2-(Ethoxycarbonyl)prop-2-en-1-yl phenyl sulfone (1).*² Ethyl methacrylate (7.50 mL, 60 mmol) (Note 1) and absolute ethanol (120 mL) are added to a 250-mL, three-necked, round-bottomed flask (Note 2) equipped with a magnetic stir bar, a glass stopper, a thermometer, and an argon inlet adaptor. The mixture is cooled to 0 °C in an ice bath, the stopper is removed, iodine (18.1 g, 71 mmol) and benzenesulfinic acid sodium salt (22.7 g, 126 mmol) are added with the aid of a plastic funnel, and the stopper is replaced. The temperature of the mixture increases to 6–7 °C upon addition of the sodium salt. The reaction mixture is recooled to 0 °C and stirred for 5 h, then allowed to warm to room temperature. Dichloromethane (100 mL) is added and the dark brown reaction mixture is transferred to a 500-mL separatory funnel. The organic layer is washed with water (2 x 100 mL) (Note 3), and the water is back-extracted with dichloromethane (2 x 25 mL). The combined organic layer is washed with saturated sodium hydrogen carbonate solution (100 mL) and sodium dithionite (5% solution, 2 x 100 mL). The resulting yellow solution is dried over MgSO₄, filtered into a 250-mL, one-neck, round-bottomed flask and

concentrated to dryness by rotary evaporation (40 °C, 500 mbar) to yield 22.58–22.68 g (98–99%) crude adduct as a dark oil (Note 4).

After addition of a magnetic stir bar, the flask is capped with a septum, placed under an argon atmosphere, and the crude adduct is diluted with dichloromethane (35 mL). Triethylamine (16.7 mL, 120 mmol) is added dropwise by syringe over 10 min (Note 5). The resulting orange-brown mixture is stirred for 9 h at room temperature (Note 6). The reaction mixture is concentrated by rotary evaporation (35 °C, bath temperature) to about half of its original volume (Note 7), and the concentrate is charged onto a column (8 x 18 cm) of 350 g of silica gel (Note 8). The column is eluted with 500 mL of *tert*-butyl methyl ether/cyclohexane (1:4), at which time the eluent is changed to *tert*-butyl methyl ether/cyclohexane (3:7). After elution with about 1 L of the solvent mixture, the product begins to emerge, as identified by TLC analysis (Note 6). The eluting solvent is changed to *tert*-butyl methyl ether/cyclohexane (1:1), and the product fractions are collected. Combination of the fractions, concentration by rotary evaporation (35 °C, bath temperature), and vacuum drying afforded 13.45–13.85 g of **1** as a colorless oil (88–90% yield) (Note 9).

B. Ethyl 2- $\{[(1S,2R,3R,5S)$ -2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)methyl}acrylate (**2**).^{3,4} (+)- α -Pinene (7.14 mL, 45 mmol), *N,N*-dimethylacetamide (0.42 mL, 4.5 mmol) (Note 10) and dichloromethane (30 mL) are added to a 100-mL, three-necked, round-bottomed flask equipped with a large, oblong magnetic stir bar, a reflux condenser with an argon inlet, a glass stopper, and a straight glass stopcock fitted with rubber septum. The stirred mixture is cooled to 0 °C in an ice bath, and catecholborane (12.0 mL, 113 mmol) (Note 11) is added dropwise via syringe by placing the syringe needle through the septum on the open stopcock. The stopcock is closed, the ice bath is removed and colorless reaction mixture is heated to reflux for 5 h (Note 12). The mixture is cooled to 0 °C, and methanol (3.0 mL, 74 mmol) is carefully added [*CAUTION: vigorous evolution of hydrogen gas*] to quench the excess of catecholborane, and the resulting mixture is warmed to room temperature and stirred for 15 min.

2-(Ethoxycarbonyl)prop-2-en-1-yl phenyl sulfone **1** from Step A (13.7 g, 54 mmol) is added via syringe, and the mixture is heated to reflux. Air (40 mL, 0.33 mmol O₂) (Note 13) is introduced over 1 h by a syringe pump with the needle of the syringe placed through the stopcock and immersed just under the surface of the liquid. After 15–20 min, the clear yellow mixture turns black (Notes 12 and 14). After 1 h, the mixture is cooled and

the solvent is removed by rotary evaporation (35 °C, bath temperature). The resulting black oil is dissolved in a minimum of dichloromethane (~20 mL). The solution is charged onto a column (8 x 9 cm) of 200 g silica gel, and the column is eluted with *tert*-butyl methyl ether/cyclohexane 1:19. Fractions containing the product (Note 15) are concentrated by rotary evaporation (35 °C, bath temperature) and dried under high vacuum to provide 8.70–8.75 g compound **2** (77–78%) as a colorless oil (Note 16).

2. Notes

1. The submitters purchased ethyl methacrylate (99%), iodine (99%) and benzenesulfinic acid sodium salt (97%) from Fluka Chemie GmbH. The checkers purchased ethyl methacrylate (99%) and benzenesulfinic acid sodium salt (98%) from Aldrich, and iodine (Certified A.C.S.) from Fischer Scientific. All reagents were used as received.

2. The apparatus is dried in an oven at 130 °C for 24 h, cooled in a dessicator, and maintained under an argon atmosphere during the course of the reaction.

3. Both layers are dark. Use of a flashlight helps to identify the phase boundary. Small additional amounts of water and dichloromethane can be added if the phases do not separate after the first extraction.

4. The intermediate adduct is $\text{PhSO}_2\text{CH}_2\text{C}(\text{I})(\text{CH}_3)\text{CO}_2\text{Et}$: $R_f = 0.58$, 1/1 *tert*-butyl methyl ether/cyclohexane. ^1H NMR (300 MHz, CDCl_3): δ : 1.34 (t, $J = 7.2$ Hz, 3 H), 2.45 (s, 3 H), 3.95 (d, $J = 13.8$ Hz, 1H), 4.22–4.32 (m, 2 H), 4.51 (d, $J = 13.8$ Hz, 1 H), 7.60 (m, 2 H), 7.68 (m, 1 H), 7.92 (m, 2 H). The sample becomes a dark solid upon standing in the freezer.

5. The reaction mixture warms during the addition, so the rate of addition must be slow enough to keep the temperature well below the reflux point.

6. Reaction progress can be monitored by TLC analysis on silica eluting with 1/1 *tert*-butyl methyl ether/cyclohexane (UV lamp visualization): starting adduct $R_f = 0.58$; product **1** $R_f = 0.35$.

7. Salts may begin to precipitate towards the end of the concentration. These are loaded onto the column along with the residual liquid.

8. The submitters used SDS silica gel (40-63 mm). The checkers used standard grade silica gel (40-63 mm) from Sorbent Technologies, Inc.

9. ^1H NMR (300 MHz, CDCl_3)² δ : 1.15 (t, $J = 7.1$ Hz, 3 H), 4.00 (q, $J = 7.1$ Hz, 2 H), 4.15 (d, $J = 0.8$ Hz, 2 H), 5.89 (narrow q, $J = 0.8$, 0.6 Hz, 1 H), 6.49 (d, $J = 1$ Hz, 0.6 H), 7.52 (m, 2 H), 7.62 (m, 1 H), 7.84 (m, 2 H);

^{13}C NMR (75 MHz, CDCl_3) δ : 13.9, 57.4, 61.4, 128.6, 128.9, 129.0, 133.2, 133.8, 138.2, 164.6. The submitters report that the product can be further purified by distillation in a Kugelrohr oven; bp 90–95 °C (6 mmHg).

10. The submitters purchased α -pinene (97%) and *N,N*-dimethylacetamide (99%) from Fluka Chemie GmbH. The checkers purchased (*R*)-(+)- α -pinene (98%, 91% ee) from Aldrich and *N,N*-dimethylacetamide (99%) from J. T. Baker. These were used as received.

11. The quality of the catecholborane is crucial for success. The submitters purchased catecholborane from BASF corporation, Mount Olive, NJ, USA and distilled it (bp 50 °C, 50 mmHg) prior to use. The checkers used catechol borane (98%) directly from a fresh bottle purchased from Aldrich.

12. The progress of the hydroboration reaction and the radical allylation reaction can be monitored by GC analysis on an Agilent MP-1 methyl siloxane capillary column (19091Z-413E, 30 m x 0.32 mm); temperature ramp, 10 °C per min from 50 °C to 315 °C. T_R ; pinene, 3.59 min; hydroboration adduct, 15.21 min; **1**, 15.29 min; **2**, 12.68 min. The submitters used a CE instrument, MEGA Series HRGC fitted with an Optima delta-3 0.25 μm fused silica capillary column from Macherey-Nagel, 30 m x 0.25 mm; temperature ramp, 6 °C per min from 60 °C to 280 °C; T_R pinene, 7.38 min; **1**, 31.53 min; **2** = 24.86 min.

13. The submitters report that initiation with di-*tert*-butyl hyponitrite in refluxing dichloromethane afforded a similar reaction yield.³

14. GC analysis at this point (Note 12) indicates that the reaction is complete. The checkers observed the black color after 15–20 min, while the submitters observed the color change after about 1 h.

15. Thin layer chromatography (TLC) analysis is used to identify product fractions. TLCs are performed by using Merck silica gel 60 F₂₅₄ analytical plates; detection with UV or by dipping in a solution of KMnO_4 (3 g), K_2CO_3 (20 g), NaOH 5% (5 mL) in H_2O (300 mL) and subsequent heating. Product R_f 0.62 in *tert*-butyl methyl ether/cyclohexane (1:9).

16. ^1H NMR (300 MHz, CDCl_3) δ : 0.74 (d, J = 9.5 Hz, 1 H), 0.97 (s, 3 H), 1.00 (d, J = 7.1 Hz, 3H), 1.16 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.40 (ddd, J = 13.3, 5.9, 2.6 Hz, 1 H), 1.66 (quintd, J = 7.1, 1.9 Hz, 1 H), 1.75 (td, J = 5.7, 1.9 Hz, 1 H), 1.82–1.97 (m, 2 H), 2.04 (tdd, J = 11.4, 3.5, 2.1 Hz, 1 H), 2.13 (ddd, J = 13.5, 9.3, 0.7 Hz, 1 H), 2.27 (dtd, J = 9.5, 6.2, 2.1 Hz, 1 H), 2.51 (ddd, J = 13.5, 5.1, 1.0 Hz, 1 H), 4.19 (m, 2 H), 5.52 (dd, J = 1.7, 1.0 Hz, 1 H), 6.11 (d, J = 1.7 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 14.1, 21.4, 22.9, 28.0, 34.0, 34.2, 34.6, 38.8, 41.9, 43.4, 43.5, 48.2, 60.4, 125.3,

139.8, 167.3; MS (EI): m/z (%): 250 [M^+], 235, 207, 194, 176, 137, 121, 107, 93, 81, 67, 55; $[\alpha]_D^{20}$ -31.5 (c, 1.0, CHCl_3). If desired, the product can be further purified by vacuum distillation (bp 113–114 °C, 0.45 mmHg) to provide a clear oil; Anal. calcd for $\text{C}_{16}\text{H}_{26}\text{O}_2$: C, 76.75; H, 10.47. Found: C, 76.77; H, 10.41.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

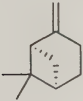
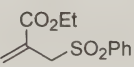
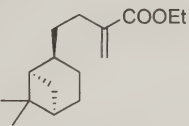
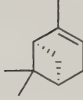
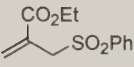
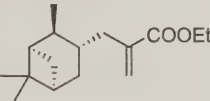

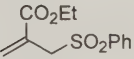
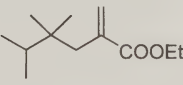
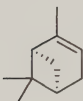
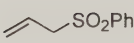
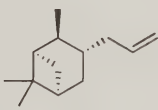
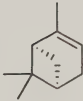
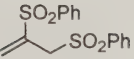
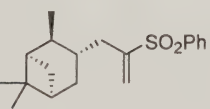
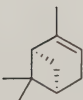
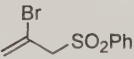
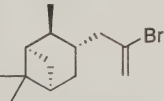
Here we describe an efficient one-pot radical hydroallylation of an alkene under tin-free conditions.^{3,4} *B*-Alkylcatecholboranes are easily prepared by hydroboration of alkenes with catecholborane according to the efficient and cost-effective conditions developed by Fu.⁵ These are used as radical precursors in a fragmentation process where the resulting benzenesulfonyl radical can sustain the radical chain. This methodology has proven to be an effective alternative to radical reactions mediated by toxic tin reagents. Interestingly, this radical approach complements nicely Knochel’s procedure for the allylation of organoboranes, which requires transmetalation to organozinc derivatives.⁶

Oxygen-centered radicals react efficiently with *B*-alkylcatecholboranes.⁷ The use of oxygen from air as the radical initiator is efficient for a large-scale reaction. Care is always required when oxygenating warm organic solvents. In this reaction, slow syringe pump addition of air is a suitable way to continuously provide the small amounts of oxygen needed for initiation. This transformation can be carried out under mild conditions and is tolerant of a wide range of organic functionalities.

Typical results of this reductive allylation (hydroallylation) of alkenes are shown in Table 1. The allylated products were obtained in satisfactory to excellent yields by using only 1.2 equivalents of the allyl sulfones with primary, secondary and tertiary alkyl radicals (Entries 1-3). The unsubstituted allyl sulfone also reacts under these conditions and provides the volatile allylated product in moderate isolated yield (Entry 4). Finally, allylic sulfones bearing a sulfonyl group ($\text{Y} = \text{PhSO}_2$) and a bromine atom ($\text{Y} = \text{Br}$) reacted equally well (Entries 5-6). The stereochemical outcome of

all these reactions is rationalized in a straightforward manner, both the hydroboration and the radical reaction occur from the less hindered face of the alkene and of the radical, respectively.

Table 1

Entry	Alkene	Trap	Product	Yield	dr
1				62 % ^a	90/10
2				80 % ^b	>98/2
3				65 % ^a	
4				52 % ^a	95/5
5				89 % ^a	96/4
6				58 % ^a	96/4

a) 2-3 mmol scale b) 45 mmol scale

1. University of Bern, Department of Chemistry and Biochemistry, Freiestrasse 3, 3000 Bern 9 (Switzerland).
2. Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1990**, *55*, 5977.
3. Schaffner, A.-P.; Renaud, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 2658.
4. Schaffner, A.-P.; Becattini, B.; Ollivier, C.; Weber, V.; Renaud, P. *Synthesis* **2003**, *17*, 2740.
5. Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 3224.
6. Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 2748.
7. Schaffner, A.-P.; Renaud, P. *Eur. J. Org. Chem.* **2004**, 2291.

Appendix

Chemical Abstracts nomenclature; (Registry Number)

Ethyl 2-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)methyl]propenoate;
(183623-93-0)

2-(Ethoxycarbonyl)prop-2-en-1-yl phenyl sulfone; (89295-32-9)

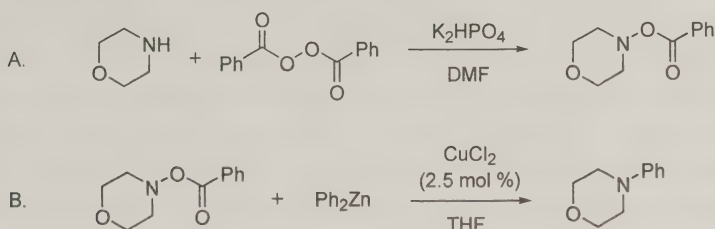
Ethyl methacrylate: 2-Methyl-2-propenoic acid, ethyl ester; (97-63-2)

Benzenesulfinic acid, sodium salt: Sodium benzenesulfinate; (873-55-2)

(+)- α -Pinene: (1*R*)-2,6,6-Trimethyl-bicyclo[3.1.1]hept-2-ene; (7785-70-8)

Catecholborane: 1,3,2-Benzodioxaborole; (274-07-7)

COPPER-CATALYZED ELECTROPHILIC AMINATION OF DIORGANOZINC REAGENTS: 4-PHENYLMORPHOLINE



Submitted by Ashley M. Berman and Jeffrey S. Johnson.¹

Checked by George Nora and Marvin J. Miller.

1. Procedure

A. *4-Benzoyloxymorpholine*. A 500-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar is charged with benzoyl peroxide (12.11 g, 50 mmol), dipotassium hydrogen phosphate (13.06 g, 75 mmol), and *N,N*-dimethylformamide (125 mL). The suspension is stirred and morpholine (5.20 mL, 59.4 mmol) (Note 1) is added via syringe in one portion (Note 2). The flask is capped with a septum and the suspension is stirred at ambient temperature for 1 h, during which time a gradual discoloration of the reaction mixture from clear to yellow occurs. Deionized water (200 mL) is added and the contents are stirred vigorously for several min until all solid has dissolved. The reaction mixture is transferred to a 1-L separatory funnel and extracted with ethyl acetate (1 x 150 mL). The organic phase is collected and washed with saturated aqueous NaHCO_3 solution (2 x 100 mL). All of the aqueous fractions are combined and extracted with ethyl acetate (3 x 100 mL). All of the organic fractions are combined and washed with three 100-mL portions of deionized water, 100 mL of brine, dried over MgSO_4 , filtered, and concentrated by rotary evaporation. The resulting pale-yellow solid is purified by flash column chromatography (Note 3), to yield 7.28–8.03 g (70.3–77.5%) of 4-benzoyloxymorpholine as a white, crystalline solid (Note 4).

B. *4-Phenylmorpholine*. An oven-dried 250-mL, one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a septum is maintained under an inert atmosphere of argon and charged with

zinc chloride (2.04 g, 15 mmol), and anhydrous tetrahydrofuran (27 mL) (Note 5). The solution is stirred and cooled in an ice-bath. Phenylmagnesium bromide (30 mL, 30 mmol) is added via syringe in one portion (Note 6). The resulting orange-colored solution is stirred for an additional 30 min in the ice-bath prior to use.

An oven-dried 1-L, two-necked, round-bottomed flask equipped with a thermometer, a septum, and a Teflon-coated magnetic stir bar is maintained under an inert atmosphere of argon and charged with 4-benzoyloxy-morpholine (5.18 g, 25 mmol), copper(II) chloride (0.084 g, 0.625 mmol), and anhydrous tetrahydrofuran (250 mL) (Note 7). The solution is stirred and cooled in an ice-bath. The previously generated diphenylzinc solution is added via cannula over the course of 5–10 min at a rate such that the internal temperature does not exceed 5 °C. The resulting light brown solution is stirred for 1.5 h in the ice-bath. Diethyl ether (250 mL) is added and the reaction mixture is transferred to a 1-L separatory funnel. The reaction mixture is washed with saturated aqueous NaHCO₃ solution (3 x 200 mL) (Note 8), brine (1 x 100 mL), and concentrated by rotary evaporation. The resulting yellow oil is dissolved in diethyl ether (100 mL) and the solution is extracted with 10 % aqueous HCl solution (3 x 50 mL). The aqueous extracts are basified with 10 % aqueous NaOH solution (200 mL) and extracted with dichloromethane (3 x 100 mL). The organic fraction is washed with 150-mL of brine, dried over Na₂SO₄, filtered, and concentrated by rotary evaporation to yield 2.73 g (67%) of 4-phenylmorpholine as an off-white, crystalline solid (Note 9).

2. Notes

1. Benzoyl peroxide (97%) was purchased from Aldrich Chemical Company. Dipotassium hydrogen phosphate was purchased from Fisher Scientific. *N,N*-Dimethylformamide (99%) and morpholine (99%) (d = 0.996 g/mL @ 25 °C) were purchased from Acros. All reagents were used as received.

2. A slight exotherm develops approximately 30 seconds after the completion of addition of morpholine.

3. Flash column chromatography was performed on a silica gel column (20 cm length x 18 cm width, 180 g of silica gel) eluting with 50% EtOAc:hexanes. Collected fractions were analyzed by thin layer chromatography (TLC), eluting with 50% EtOAc:hexanes (R_f = 0.35 for 4-benzoyloxymorpholine). Visualization was accomplished with UV light and

on spraying with aqueous ceric ammonium molybdate solution followed by heating.

4. Analytical data for 4-benzoyloxymorpholine: mp 82–84 °C, lit mp 81–82 °C;² IR (Nujol, cm⁻¹) 2924, 2852, 1730, 1599, 1456, 1377, 1315, 1269, 1248, 1178, 1165, 1101, 1084, 1066, 1049, 1007, 922, 858, 712; ¹H NMR (400 MHz, CDCl₃) δ: 3.03 (br t, *J* = 9.4 Hz, 2 H), 3.43 (br d, *J* = 9.3 Hz, 2 H), 3.85 (br t, *J* = 11.2 Hz, 2 H), 3.96 (br d, *J* = 10.7 Hz, 2 H), 7.45–7.41 (m, 2 H), 7.58–7.53 (m, 1 H), 8.00–7.98 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ: 57.0, 65.8, 128.4, 129.2, 129.4, 133.1, 164.6. Anal. Calcd for C₁₁H₁₃NO₃: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.96; H, 6.40; N, 6.67. The checkers noted that storage of this compound in the freezer (-10 °C) or at room temperature resulted in discoloration. The checkers recommend that it be used immediately upon formation.

5. Zinc chloride (98%) was purchased from Riedel-de-Haën and because it is very hygroscopic, it was dried under vacuum (0.1 mmHg) at 150 °C for 12 h prior to use. Tetrahydrofuran was dried by passage through a column of neutral alumina under nitrogen prior to use.

6. Phenylmagnesium bromide was purchased from Aldrich Chemical Company as a 1.0 M solution in tetrahydrofuran, and was used as received. The checkers noted that if the color does not change upon addition of the Grignard reagent, then the reaction does not proceed.

7. Copper(II) chloride (97%) was purchased from Aldrich Chemical Company and was used as received. Upon addition of the copper (II) chloride the solution turned a light green.

8. Copious formation of a white precipitate accompanied the initial wash with saturated aqueous NaHCO₃ solution.

9. Analytical data for 4-phenylmorpholine: mp 50–52 °C, (lit mp 53–54 °C);³ IR (Nujol, cm⁻¹) 2922, 2854, 1601, 1498, 1458, 1377, 1231, 1126, 928, 771, 758, 690; ¹H NMR (400 MHz, CDCl₃) δ: 3.16–3.13 (m, 4 H), 3.86–3.84 (m, 4 H), 6.92–6.85 (m, 3 H), 7.30–7.24 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ: 49.4, 66.9, 115.7, 120.0, 129.2, 151.3. Anal. Calcd for C₁₀H₁₃NO: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.71; H, 8.03; N, 8.52. The checkers report that the procedure, when checked at half-scale, provided a 71% yield.

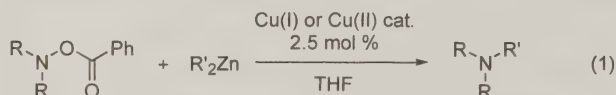
Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

Amines are of fundamental interest in many areas of chemistry. Consequently, the development of methodology for the facile preparation of these compounds continues to be a topical area of research.⁴ Among the modern methods for the preparation of amines, the Buchwald-Hartwig coupling is a convenient and general route to aryl amines, and represents the benchmark in catalyzed nucleophilic amination.^{5,6} Electrophilic amination of nonstabilized carbanions is an alternative approach, and is noteworthy for its use of the *umpolung* strategy for C-N bond construction.^{7,8} Generally, electrophilic amination has been limited to only the most reactive carbon donors (RLi and RMgX reagents), and yields of amine products are modest. Reports of transition-metal catalyzed methods present a possible solution to these problems, but have as yet been limited to the preparation of primary aniline derivatives.^{9,10}

The copper-catalyzed electrophilic amination of diorganozinc reagents presented here allows for the expeditious preparation of tertiary amines under mild reaction conditions (eq 1).¹¹

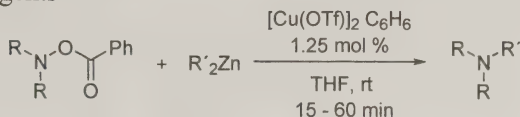


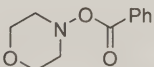
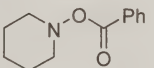
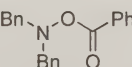
The *O*-benzoyl hydroxylamines employed are easily prepared from the corresponding secondary amines upon treatment with benzoyl peroxide, and show good stability: they are crystalline solids which can be purified via column chromatography and stored indefinitely in a freezer without decomposition or loss of reactivity. These reagents consequently represent a convenient source of sp^3 -hybridized nitrogen electrophiles for the direct delivery of R_2N^+ synthons. The secondary amine oxidation that is used here is a modification of a protocol originally reported by Ganem.² Elevated temperatures were found to be unnecessary and the use of DMF as reaction solvent provided higher yields than diethyl ether.

The amination reaction is quite general in the nucleophilic component, with both sp^2 - (aryl, heteroaryl) and sp^3 -hybridized (alkyl, benzyl) carbanions undergoing coupling in uniformly high yields (Table 1). On a scale of <1 mmol, it is convenient to conduct the reaction at ambient temperature; however, the 25-mmol preparation conducted in this procedure should be performed in an ice bath to minimize a deleterious exotherm.

The R_2Zn reagents employed are prepared via transmetallation from the corresponding $RMgX$ or RLi with 0.5 equivalents of $ZnCl_2$, and are used *in situ* without isolation or purification.

Table 1. Scope of the Copper-Catalyzed Amination of Diorganozinc Reagents^a



entry	$R_2N-OC(O)Ph$	R'	% yield ^b
1		<i>p</i> -MeOC ₆ H ₄	93
2		<i>o</i> -MeC ₆ H ₄	94
3		2-pyridyl	71
4		Bn	80
5		Ph	91
6		Ph	94
7		Bn	91
8		Et	91
9		<i>t</i> -Bu	98

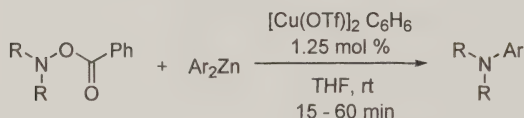
^a Unless otherwise noted, 1.1 equiv of R_2Zn were employed. Reactions were run on a 0.50 mmol scale of the starting $R_2N-OC(O)Ph$. ^b Isolated yield of product (average of at least two experiments). Yield is based on the starting $R_2N-OC(O)Ph$.

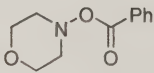
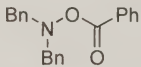
Functionalized tertiary aryl amines can also be prepared when functionalized Ar_2Zn reagents are employed.¹² The latter are generated *in situ* from the corresponding aryl iodides via a simple Mg/I exchange/transmetallation sequence.¹³ The reaction shows good functional group tolerance, with nitrile, ester, halide, triflate, and nitro functionalities all accommodated (Table 2).

In conclusion, the copper-catalyzed amination of diorganozinc reagents represents a convenient and general route to tertiary amines. The reaction is noteworthy for the mild reaction conditions employed and ease of

product purification (acid/base extractive workup). The catalyst is cheap and requires no exogenous supporting ligand. Such procedures may find utility as a complement to Buchwald-Hartwig coupling reactions.

Table 2. Scope of the Copper-Catalyzed Amination of Functionalized Diarylzinc Reagents^a



entry	R ₂ N-OC(O)Ph	Ar	% yield ^b
1		<i>p</i> -NCC ₆ H ₄	76
2		<i>p</i> -EtO ₂ CC ₆ H ₄	77
3		<i>p</i> -ClC ₆ H ₄	93
4		<i>p</i> -TfOC ₆ H ₄	95
5		<i>o</i> -O ₂ NC ₆ H ₄	83
6		<i>p</i> -NCC ₆ H ₄	95
7		<i>p</i> -EtO ₂ CC ₆ H ₄	99
8		<i>o</i> -O ₂ NC ₆ H ₄	97

^a 1.1equiv of Ar₂Zn were employed. Reactions were run on a 0.25 mmol scale of the starting R₂N-OC(O)Ph. ^b Isolated yield of product (average of at least two experiments). Yield is based on the starting R₂N-OC(O)Ph.

1. Department of Chemistry, University of North Carolina, Chapel Hill, NC 27599-3290, E-mail: jsj@unc.edu.
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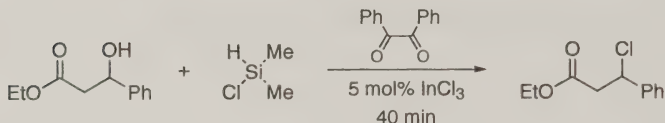
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Appendix

Chemical Abstracts Nomenclature (Registry Number)

- Benzoyl peroxide: Dibenzoyl peroxide; (94-36-0)
 Phenylmagnesium bromide: Magnesium, bromophenyl-; (100-58-3)
 4-Benzoyloxymorpholine; (5765-65-1)
 4-Phenylmorpholine: (92-53-5)

**DIRECT CHLORINATION OF ALCOHOLS: SYNTHESIS OF
ETHYL 3-CHLORO-3-PHENYLPROPANOATE
[Benzenepropanoic acid, β -chloro-, ethyl ester]**



Submitted by Makoto Yasuda, Satoshi Yamasaki, Yoshiyuki Onishi, and Akio Baba.¹

Checked by John R. Heemstra, Jr. and Scott E. Denmark.

1. Procedure

Caution! This reaction generates hydrogen (H_2) gas and therefore should be conducted in an efficient hood.

A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stir bar, a glass stopper, a Teflon-coated thermocouple, and a Leibig reflux condenser fitted with an inert gas inlet tube that is attached to a nitrogen manifold. The flask is flame-dried under vacuum, (0.2 mmHg) flushed with nitrogen, cooled to room temperature, and maintained under a slightly positive pressure of nitrogen. The flask is charged with InCl_3 (0.775 g, 3.5 mmol) (Note 1), which is then dried by heating the bottom of the flask with a hot air gun under vacuum (0.2 mmHg) for 2 min (Note 2). The flask is then refilled with nitrogen and kept under a slightly positive pressure. The glass stopper is removed and to the flask are added benzil (14.7 g, 70 mmol) (Note 3), dichloromethane (140 mL) (by syringe) (Note 4), and ethyl 3-hydroxy-3-phenylpropanoate (by syringe) (13.6 g, 70 mmol) (Note 5). Chlorodimethylsilane (HSiMe_2Cl) (7.28 g, 77 mmol) is added to the resulting mixture by syringe through an open neck while stirring (Note 6). The stopper is replaced and gentle evolution of gas (H_2) starts in a few minutes (Note 7). The extent of the gas evolution gradually increases and the reaction temperature slowly increases (Note 8).

After 35 min, gas evolution ceases (Note 9), indicating the end of the reaction. The solution is stirred for 5 min further (40 min total after addition

of chlorodimethylsilane), whereupon water (100 mL) is added to the flask and the mixture is transferred into a 1-L separatory funnel containing diethyl ether (200 mL). After the mixture is shaken, the organic layer is separated and the aqueous layer is extracted with diethyl ether (1 x 100 mL, 1 x 60 mL). The combined organic extracts (yellow solution) are dried over anhydrous magnesium sulfate (MgSO_4), filtered and concentrated at reduced pressure by rotary evaporation (30 °C/14 mmHg). The residue is diluted with hexane (20 mL) and cooled in an ice-bath to give a precipitate, which is filtered (Note 10). The filtrate is concentrated at reduced pressure by rotary evaporation (30 °C/14 mmHg) to afford a yellow oil.

The oil is loaded onto a column (4 cm diam x 14 cm height) of 100 g of silica gel (Note 11) with hexane. Using compressed air, the column is eluted with hexane (250 mL) (Note 12) and then ethyl acetate (300 mL) (Note 13). The ethyl acetate fraction (yellow solution) is concentrated by rotary evaporation (30 °C/14 mmHg) to afford 19.08 g of yellow liquid (Note 14). The liquid is distilled at reduced pressure to give 14.0 g (94%) of ethyl 3-chloro-3-phenylpropanoate (90 °C/0.2 mmHg) as a yellow oil (Notes 15-18).

2. Notes

1. InCl_3 (98%) was obtained from Aldrich Chemical Company, Inc., and used as received.
2. InCl_3 is hygroscopic and this procedure gives dry InCl_3 .
3. Benzil (98%) was obtained from Aldrich Chemical Company, Inc., and used as received.
4. Dry dichloromethane was obtained from Wako Pure Chemical Industries, Ltd. (Japan), and used as received.
5. The reaction temperature does not change during this process. A yellow solution with a precipitate is observed.
6. Chlorodimethylsilane (98%) was obtained from Aldrich Chemical Company, Inc., and used as received. The bottle of the reagent should be cooled at -30 °C in freezer before the syringe transfer operation.
7. The evolution of H_2 can be checked by bubbler and is seen in the flask as bubbles.

8. Internal temperatures: 19 °C (0-6 min), 21 °C (10 min), 26 °C (20 min), 30 °C (25 min), 31 °C (30 min), 30-29 °C (35-40 min).

9. The gas (H_2) evolves constantly for about 30 min and ceases at 35 min. The period of the time is shorter for smaller scale reactions.

10. The precipitate is separated by vacuum filtration using 60 mm Büchner funnel. The solid is carefully washed with cold hexane (50 mL). The separated pale yellow solid is pure benzil (10.1 g).

11. Silica gel was purchased from Silicycle (SiliaFlash P60 (40-63 μ , 60 Å pore size)). For TLC analysis, EMD Chemicals, Inc. silica gel 60 F₂₅₄ TLC plates were used, with hexane/Et₂O, 7:3 as eluent. The starting alcohol (ethyl 3-hydroxy-3-phenylpropanoate), the chlorinated product (ethyl 3-chloro-3-phenylpropanoate), and benzil have R_f values of ca. 0.28, 0.66, and 0.57, respectively.

12. The column is eluted with hexane until a few drops of yellow solution come out. This process effectively separates silyl by-product.

13. A yellow-colored solution comes out.

14. The 1H NMR spectrum shows that the liquid contains the desired chloride and benzil (79:21), along with a small amount of silyl species.

15. A forerun (10 drops) is collected and discarded to avoid contamination by silyl species.

16. The purity of the product was found to be 94%. The major contaminants detected by 1H NMR (500 MHz) spectroscopic analysis are benzil (2%) and ethyl 3-phenyl-2-propenoate (4%).

17. The residue after distillation contains mostly benzil. The pure benzil (2.47 g) is recovered from the residue by vacuum filtration and is washed with cold hexane. A total of 12.57 g (86%) of benzil is recovered (Note 11).

18. The checkers obtained an analytically pure sample of the product as follows: a 300-mg portion of the product was purified by silica gel column chromatography (2 cm diam x 11 cm height, 20 g) (Note 12) with hexane/ CH_2Cl_2 , 2:1 (200-300 mL). In this solvent system the desired product has an R_f = 0.33 and the elimination product an R_f = 0.23. Concentration of the product-containing fractions (30 °C/14 mmHg) provided 275 mg of ethyl 3-chloro-3-phenylpropanoate, which was purified by bulb-to-bulb distillation to afford 133 mg of analytically pure material. Physical properties of the purified product are as follows: 1H NMR (500

MHz, CDCl₃) δ : 1.24 (t, J = 7.1 Hz, 3 H), 3.03 (ABX, J_{AB} = 15.9 and J_{BX} = 5.8 Hz, 1 H), 3.17 (ABX, J_{AB} = 15.9 and J_{AX} = 9.1 Hz, 1 H), 4.16 (m, 2 H), 5.35 (dd, J = 5.9 and 9.0 Hz, 1 H), 7.30–7.43 (m, 5 H); ¹³C NMR (125 MHz, CDCl₃) δ : 14.0, 44.8, 58.1, 60.9, 126.9, 128.67, 128.74, 140.2, 169.5; IR (neat) cm⁻¹: 3454 (m), 3066 (m), 3034 (m), 2983 (s), 2938 (s), 2906 (m), 2360 (w), 1955 (w), 1883 (w), 1740 (s), 1604 (m), 1587 (m), 1495 (m), 1455 (m), 1367 (s), 1333 (s), 1272 (s), 1196 (s), 1159 (s), 1097 (m), 1021 (s), 948 (s); MS (EI, 70 eV) m/z (%): 212 (M⁺, 43), 183 (28), 167 (17), 149 (19), 138 (84), 125 (89), 105 (100), 91 (14), 77 (47), 63 (11); HRMS (EI, M⁺) m/z calcd for C₁₁H₁₃ClO₂: 212.0604, found: 212.0596. Anal. calcd for C₁₁H₁₃ClO₂: C, 62.12; H, 6.16; Cl, 16.67. Found: C, 62.17; H, 6.16; Cl, 16.56.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described herein provides a useful method for chlorination of alcohols under mild and neutral conditions.³ Even an acid sensitive hydroxy ester (ethyl 3-hydroxy-3-phenylpropanoate) is cleanly converted into the desired chloride. For this substrate, conventional chlorination methods⁴ in which strong protic acids are generated *in situ* using PCl₃ or PCl₅ give low yield of the chloride contaminated with ethyl 3-phenyl-2-propenoate that forms through β -elimination.³





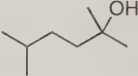
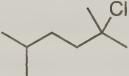


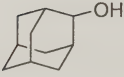
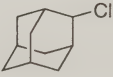
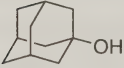
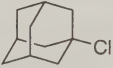
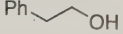
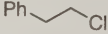
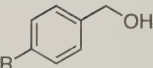
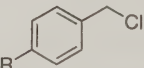


Indium trichloride (InCl₃) has moderate Lewis acidity and oxophilicity as compared with typical Lewis acids such as aluminum halides or boron halides.⁵⁻⁷ This character enables InCl₃ to catalyze the reactions of carbonyls or alcohols.^{8,9}

In the alcohol/HSiMe₂Cl/InCl₃/benzil system, role of benzil is significant. When benzil is not included, hydro-dehydroxylation (reduction) occurs through the formation of the hydrodimethylsilyl ether with release of

HCl.¹⁰ The addition of benzil changes the reaction pathway to form the chlorodimethylsilyl ether with release of H₂. Although benzil is used as an equimolar additive, about 80% of the benzil can easily be recovered. The amount of benzil can be reduced for certain substrates, but the use of a stoichiometric amount leads to faster reaction rates, higher yields, and broader substrate scope.

The generality of this chlorination method is summarized in Table 1. Various secondary and tertiary alcohols are converted into the corresponding

Table 1. Chlorination of Various Alcohols

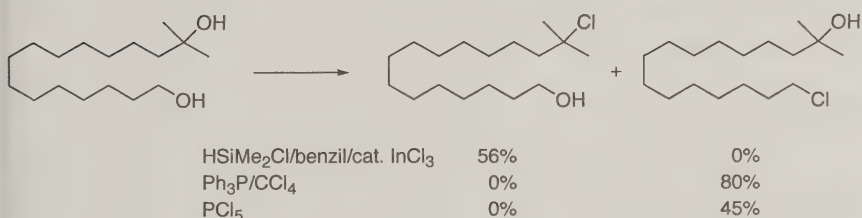
entry	alcohol	time/ h	product	yield/ %
1		6		100
2		15		68
3		9		100
4		23		71
5		91		98
6		82		93
7		24		0
8		R = H		80
9		R = Cl		92
10		R = Me		83
11		R = NO ₂		97
12		R = COOEt		77
13		2.5		91 (<2% ee)

chlorides in high yields (entries 1-6). A primary alcohol (2-phenylethanol) does not give the desired product (entry 7). However, effective transformation proceeds in the reaction with benzylic alcohols which bear

electron-withdrawing or donating substituents (entries 8-10). Nitro and ester groups tolerate these reaction conditions to furnish the corresponding chlorides (entries 11 and 12). The enantiomerically pure alcohol (1-phenylethanol) gives racemic 1-phenylethyl chloride (entry 13). These results suggests that the reaction proceeds via a carbocationic intermediate.

Selective chlorination at the tertiary site of a diol that contains both primary and tertiary alcohols illustrates the unique selectivity of this chlorination system (Scheme 1). On the contrary, conventional chlorination systems such as $\text{PPh}_3/\text{CCl}_4$ or PCl_5 afford the primary chloride.

Scheme 1



1. Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan.
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10. Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741-7744.

Appendix

Chemical Abstracts Nomenclature; (Registry Number)

InCl₃: Indium chloride; (10025-82-8)

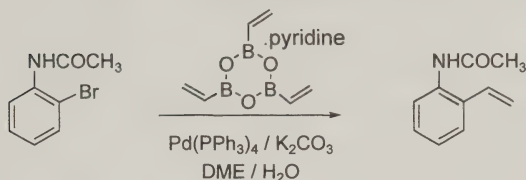
Benzil: Diphenylethanedione; (134-81-6)

Ethyl 3-hydroxy-3-phenylpropanoate: Benzenepropanoic acid, β -hydroxy-, ethyl ester; (5764-85-2)

Chlorodimethylsilane; (1066-35-9)

Ethyl 3-chloro-3-phenylpropanoate: Benzenepropanoic acid, β -chloro-, ethyl ester; (77085-24-6)

**SUZUKI-MIYaura CROSS-COUPLING: PREPARATION OF 2'-
VINYLACETANILIDE
[*N*-(2-Ethenylphenyl)acetamide]**



Submitted by Bertrand Cottineau, Albane Kessler and Donal F. O'Shea.¹
 Checked by Anuradha Gupta and Marvin J. Miller.

1. Procedure

A 500-mL, two-necked, round-bottomed flask covered in tin-foil and is equipped with a stirring bar, a reflux condenser fitted with a nitrogen inlet, and a stopper. The flask is charged with *N*-(2-bromophenyl)acetamide (10.0 g, 46.6 mmol, Note 1), ethylene glycol dimethyl ether (180 mL) (Note 2), and tetrakis(triphenylphosphine)palladium(0) (1.08 g, 0.9 mmol) (Note 3). The apparatus is maintained under an atmosphere of nitrogen during the course of the reaction. The mixture is stirred at room temperature for 20 min then potassium carbonate (6.44 g, 46.6 mmol) (Note 4) dissolved in distilled water (55 mL) is added via funnel, followed by 2,4,6-trivinylcyclotriboroxane-pyridine complex (5.6 g, 23.3 mmol) (Note 5). The reaction mixture is stirred and heated at reflux in an oil bath for 20 h, then cooled to ambient temperature. Distilled water (75 mL) is added via a funnel, and the resulting mixture is filtered on a Büchner funnel. The filtrate is transferred to a separatory funnel and extracted with diethyl ether (3 x 100 mL) (Note 6). The combined organic phases are dried over sodium sulfate, filtered on filter paper and concentrated to dryness by rotary evaporation (30 °C, 25 mmHg). The resulting yellow solid is purified by column chromatography (Note 7) affording *N*-(2-vinylphenyl)acetamide (5.9 g, 37.3 mmol) as a pale yellow solid. The solid is dissolved in a hot mixture of cyclohexane:dichloromethane (4:1) (55 mL) and the warm mixture is filtered through a Büchner funnel. The filtrate is allowed to cool to room temperature for 20 min. The flask is immersed for 30 min in an ice bath in order to complete precipitation. The resulting crystals are collected by suction filtration on a Büchner funnel, washed with cyclohexane (10 mL),

and dried under reduced pressure (15 h at 0.1 mmHg) to provide *N*-(2-vinylphenyl)acetamide (5.30 g, 71%) as a white solid (Note 8).

2. Notes

1. *N*-(2-Bromophenyl)acetamide (96%) was purchased from Aldrich Chemical Company, Inc. and was used without purification.

2. Ethylene glycol dimethyl ether (DME) was purchased from Aldrich Chemical Company, Inc. and passed through a column of Merck aluminium oxide 90 (30 g) immediately prior to use.

3. Tetrakis(triphenylphosphine)palladium(0) was used as received from Aldrich Chemical Company, Inc.

4. Potassium carbonate (99%) was used as received from Aldrich Chemical Company, Inc.

5. 2,4,6-Trivinylcyclotriboroxane-pyridine complex (purity not indicated) was used as received from Frontier Scientific, Inc.

6. Diethyl ether was used as received from Aldrich Chemical Company, Inc. (HPLC grade).

7. The yellow solid, dissolved in 20 mL of dichloromethane, was applied to 4.5 cm diameter column packed with 600 g of flash silica gel (Merck silica 60 mesh 0.040–0.063 mm). The product was eluted with diethyl ether/cyclohexane (9:1) (3.5 L). R_f of 2'-vinylacetanilide: 0.26 using the same eluting solvent and TLC aluminium sheets with silica gel 60F₂₅₄ (received from Aldrich Chemical Company, Inc.). Dichloromethane, diethyl ether and cyclohexane were used as received from Aldrich Chemical Company, Inc. (HPLC grade).

8. Analytical data: ¹H NMR (500 MHz, DMSO-*d*₆) δ : 2.05 (s, 3 H), 5.30 (dd, J = 11.0, 1.1 Hz, 1 H), 5.77 (dd, J = 17.5, 1.1 Hz, 1 H), 6.89 (dd, J = 17.5, 11.0 Hz, 1 H), 7.16–7.27 (m, 2 H), 7.37 (d, J = 7.9 Hz, 1 H), 7.61 (d, J = 7.8 Hz, 1H), 9.52 (bs, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ : 23.1, 115.3, 125.2, 125.4, 126.2, 127.9, 131.5, 132.4, 135.1, 168.5; mp: 94–95 °C (lit.^{3a} 89–90 °C); IR (KBr) cm⁻¹: 3228.8, 1648. MS (ES⁻) m/z 160.1; Anal. required for C₁₀H₁₁NO: C, 74.51; H, 6.88; N, 8.69; Found: C, 74.44; H, 6.99; N, 8.61. HPLC analysis [column: AtlantisTM C₁₈ 5 μ m 4.6 x 250 mm, elution: 80% CH₃CN 20% H₂O (pH = 4, adjusted with 100 μ L of HCO₂H in 1.1 L of water), 1 mL/min, 1300 psi, retention time 3.6 min] gives 100% purity at 200 and 254 nm.

Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

We have previously reported a synthetic methodology for the generation of substituted styrene derivatives using 2,4,6-trivinylcyclotriboroxane-pyridine complex as the vinyl source in a Suzuki-Miyaura cross-coupling protocol.² Functionalized styrenes are of considerable synthetic importance as key synthetic intermediates and for the generation of new polymeric materials. Specifically *N*-(2-vinylphenyl)-acetamide is an intermediate used for the synthesis of the indole ring system.³

Numerous palladium-catalyzed methods have been described in which aryl halides are utilized as starting substrates in reactions with a variety of reagents as sources of the alkene functionality. To date the most commonly utilized approaches have been the Heck⁴ and Stille⁵ methodologies, which use ethene and tributyl(vinyl)tin, respectively, as the vinyl provider. Vinylmagnesium bromide,⁶ trimethylvinylsilane,⁷ vinyltrimethylsiloxane,⁸ vinylpolysiloxanes,⁹ potassium vinyltrifluoroborate,¹⁰ vinylboronic acid dibutyl ester,¹¹ trivinylindium,¹² vinylbromide,¹³ and divinylaluminium-2-dimethylaminoethanolate¹⁴ have also been demonstrated as coupling reagents.

Aryl halides with *ortho*-substituents are known to be challenging substrates for cross-coupling reactions of boronic acids, therefore we chose *N*-(2-bromophenyl)acetamide as a test substrate.¹⁵ The target product has been previously synthesised by the coupling of ethene with *N*-(2-bromophenyl)acetamide using a high pressure Heck protocol.^{3a}

In our reaction the cross-coupling proceeds efficiently by using a standard coupling procedure without the need of specialized catalysts. The reaction is successful with 0.5 mole equivalent of the trivinylboronic anhydride indicating that the anhydride provides more than one of the vinyl groups for reaction. In summary, 2,4,6-trivinylcyclotriboroxane-pyridine complex serves as a versatile coupling partner with aryl halides for the generation of substituted styrenes.

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Appendix

Chemical Abstracts Nomenclature (Registry Number)

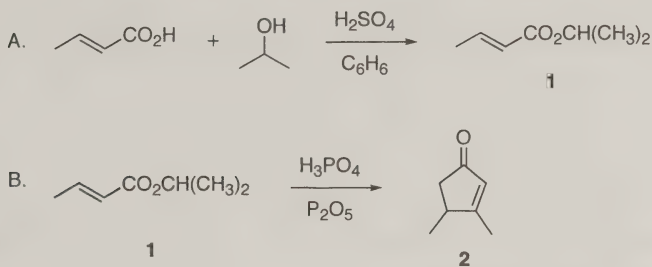
N-(2-Bromophenyl)acetamide; (614-76-6)

Tetrakis(triphenylphosphine)palladium(0); (14221-01-3)

2,4,6-Trivinylcyclotriboroxane-pyridine complex: Boron, ethenyl[(ethenylboronic acid- κ O) bimol. monoanhydridato(2-)] (pyridine)-; (95010-17-6)

N-(2-Vinylphenyl)acetamide: Acetamide, *N*-(2-ethenylphenyl)-; (29124-68-3)

FRAGMENTATION-RECOMBINATION NAZAROV CYCLIZATION: 3,4-DIMETHYLCYCLOPENT-2-EN-1-ONE



Submitted by Keith D. Schwartz and James D. White.¹
Checked by Shin-ya Tosaki and Masakatsu Shibasaki.

1. Procedure

A. *Isopropyl (E)-but-2-enoate (1)*. A 500-mL round-bottomed flask is fitted with a Soxhlet extractor containing magnesium sulfate (10 g) in a cellulose extraction thimble. Atop the extractor is a reflux condenser fitted with a rubber septum and an argon line. The flask is charged with crotonic acid (17.00 g, 197.5 mmol), isopropanol (106 mL, 1.39 mol), concentrated sulfuric acid (2.5 mL) and benzene (30 mL) (Note 1). The mixture is heated to reflux over the MgSO₄ plug for 18 h and is then cooled to room temperature. Benzene (60 mL) is added, followed by the dropwise addition of a 10% aqueous solution of sodium bicarbonate (100 mL) while stirring. The mixture is transferred to a separatory funnel, the layers are separated, and the aqueous portion is extracted with benzene (3 x 25 mL). The organic layers are combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The solvent is evaporated under vacuum and the resulting yellow oil is purified by distillation (46–48 °C/25 mmHg) to give 17.98–18.00 g (71%) of isopropyl (*E*)-but-2-enoate (**1**) (Note 2) as a colorless oil.

B. *3,4-Dimethylcyclopent-2-enone (2)*. A three-necked, 1-L round-bottomed flask is fitted with a mechanical stirrer, a glass stopper, a rubber septum, and an argon line. The flask is charged with phosphoric acid (32.0 g) and phosphorus pentoxide (48.0 g) (Note 1). The mixture is stirred at 100 °C for 1 h, at which time it becomes homogenous. To this mixture is added the neat ester **1** (10.0 g, 78.0 mmol), and the mixture is stirred for 3 min at 100 °C. The mixture is cooled to 0 °C with an ice bath. Diethyl ether

(Et₂O, 100 mL) is added followed by the slow addition of saturated aqueous NaHCO₃ (150 mL) with vigorous stirring. Solid NaHCO₃ is then cautiously added to the mixture in small portions until foaming subsides. The contents of the flask are transferred to a separatory funnel with an additional quantity (50 mL) of Et₂O, the layers are separated, and the aqueous layer is extracted with Et₂O (3 x 60 mL). The organic layers are combined, washed sequentially with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The solvent is evaporated under vacuum and the resulting orange colored oil is purified by fractional distillation (68–69 °C/20 mmHg) to give 5.61–5.63 g (65–66 %) of 3,4-dimethylcyclopent-2-enone (**2**) (Note 3) as a colorless oil.

2. Notes

1. Crotonic acid was purchased from TCI and was used as received. Isopropanol was purchased from KANTO CHEMICAL and was used as received. Phosphorus pentoxide powder, phosphoric acid (85 wt. % solution in water), concentrated sulfuric acid, and benzene were purchased from Wako and were used as received. Diethyl ether was purchased from Showa-ether and was used as received.

2. Physical data for isopropyl (*E*)-but-2-enoate: IR (neat, cm⁻¹) 2981, 2940, 1718, 1661; ¹H NMR (500 MHz, CDCl₃) δ: 1.25 (d, *J* = 6.4 Hz, 6 H), 1.86 (dd, *J* = 7.0, 1.8 Hz, 3 H), 5.05 (septet, *J* = 6.4 Hz, 1 H), 5.81 (dq, *J* = 15.6, 1.8 Hz, 1 H), 6.95 (dq, *J* = 15.6, 7.0 Hz 1 H); ¹³C NMR (125 MHz, CDCl₃) δ: 17.9, 21.9, 67.3, 123.3, 144.1, 166.1. Purity was established by gas chromatographic analysis (Restek Rtx-20 column, flow rate 1 mL/min, temperature 45–280 °C ramped at 60 °C/min, retention time 6.49 min).

3. Physical data for 3,4-dimethylcyclopent-2-enone: IR (neat, cm⁻¹) 2965, 2927, 1712, 1684, 1619; ¹H NMR (500 MHz, CDCl₃) δ: 1.19 (d, *J* = 7.3 Hz, 3 H), 2.00 (dd, *J* = 18.6, 2.1 Hz, 1 H), 2.08 (s, 3 H), 2.64 (dd, *J* = 18.6, 6.5 Hz, 1 H), 2.81 (ddt, *J* = 7.3, 6.5, 2.1 Hz, 1 H), 5.88 (s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ: 17.0, 18.8, 38.8, 44.2, 130.3, 182.6, 208.9. Purity was established by gas chromatographic analysis (Restek Rtx-20 column, flow rate 1 mL/min, temperature 120–250 °C ramped at 50 °C/min, retention time 7.87 min).

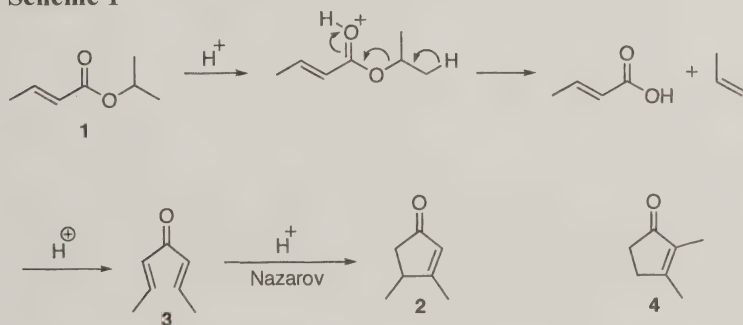
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The transformation of isopropyl (*E*)-but-2-enoate to 3,4-dimethylcyclopent-2-en-1-one represents an example of a general rearrangement of esters of α,β -unsaturated acids to cyclopentenones catalyzed by polyphosphoric acid at elevated temperature. The reaction was first reported by Conia and Lriverend,² and presumably takes place via a fragmentation-recombination-Nazarov cyclization pathway, as shown in Scheme 1. A variety of substituted cyclopent-2-en-1-ones can be prepared by this method; esters of benzoic acid give 1-indanones under the same conditions (see Table 1).

Scheme 1



3,4-Dimethylcyclopent-2-en-1-one (2) is reported to be formed in 60% yield when hepta-2,5-dien-4-one (3) is treated with phosphoric acid and 98% formic acid.³ However, a later report suggests that the major product from 3 under "Nazarov conditions" (phosphoric acid and formic acid at 90 °C) is 2,3-dimethylcyclopent-2-en-1-one (4),⁴ a result in accord with an observation made by Nozaki on Nazarov cyclization of nona-3,6-dien-5-one, which gave 2,3-diethylcyclopent-2-en-1-one.⁵ Exposure of 3 to fluoro-sulfonic acid at 0 °C gives 2 in 44% yield.⁴

3,4-Dimethylcyclopent-2-en-1-one reacts with an alkyl lithium reagent and *p*-toluenesulfonic acid to give 1,2-dimethylcyclopenta-1,3-diene which,

as its lithio or potassio derivative, has been employed in a variety of coupling reactions to produce substituted 1,2-dimethylcyclopentadienes.⁶

Bromination of 3,4-dimethylcyclopent-2-en-1-one with *N*-bromosuccinimide gives 4-bromo-3,4-dimethylcyclopent-2-en-1-one (Scheme 2).⁷ This compound, upon treatment with triethylamine, generates unstable 3,4-dimethylcyclopentadienone, which undergoes spontaneous self-Diels-Alder cycloaddition to give *endo* adduct **5**.⁸

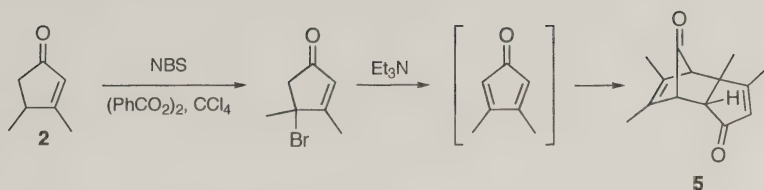
Table 1
Conversion of α,β -Unsaturated Esters to Cyclopent-2-en-1-ones
under Nazarov Conditions^a

Ester	Product	Yield (%)
		60
		60
		60
		59
		40

a) H_3PO_4 , P_2O_5

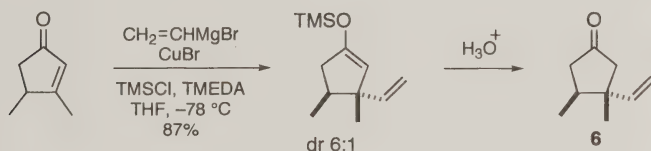
3,4-Dimethylcyclopent-2-en-1-one reacts with sodium azide in the presence of trifluoroacetic acid to give 5,6-dihydro-4,5-dimethyl-2-pyridone, a formal example of a Schmidt reaction leading to ring expansion.⁹

Scheme 2



Finally, conjugate addition of lithium divinylcuprate to 3,4-dimethylcyclopent-2-en-1-one in the presence of trimethylsilylchloride is stereoselective and yields 3-alkyl-3,4-dimethylcyclopentanone **6** after hydrolysis of the silyl enol ether (Scheme 3).¹⁰

Scheme 3



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Appendix

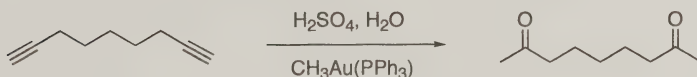
Chemical Abstracts Nomenclature (Registry Number)

Crotonic acid: 2-Butenic Acid; (3724-65-0)

Isopropyl (*E*)-but-2-enoate: 2-Butenoic acid, 1-methylethyl ester, (*2E*)-; (6284-46-4)

3,4-Dimethylcyclopent-2-enone: 3,4-Dimethyl-2-cyclopenten-1-one; (30434-64-1)

**AU(I)-CATALYZED HYDRATION OF ALKYNES:
2,8-NONANEDIONE**



Submitted by Eiichiro Mizushima,¹ Dong-Mei Cui,¹ Dilip Chandra Deb Nath,¹ Teruyuki Hayashi,*¹ and Masato Tanaka.^{1,2}
Checked by Rick L. Danheiser and Tin Yiu Lam.

1. Procedure³

2,8-Nonanedione. A 250-mL, three-necked, round-bottomed flask fitted with a rubber septum, a glass stopper, a reflux condenser equipped with an argon inlet, and a magnetic stirbar is evacuated and filled with argon, and then charged with 1,8-nonadiyne (6.3 mL, 5.0 g, 42 mmol, 1 equiv) (Note 1), methyl(triphenylphosphine)gold⁴ ($\text{CH}_3\text{AuPPh}_3$) (0.042 g, 0.088 mmol, 0.2 mol%) (Note 2), sulfuric acid (prepared by diluting 2.08 g (21.2 mmol, 0.5 equiv) of concentrated H_2SO_4 with 21 mL of water) (Note 3), and methanol (120 mL) (Note 4). The mixture is heated and stirred at reflux (oil bath temperature 70–75 °C) for 2 h, at which time analysis by gas chromatography (Note 5) shows that the conversion of 1,8-nonadiyne is complete. The reaction mixture is allowed to cool to room temperature and then transferred to a 250-mL, round-bottomed flask and most of the methanol is removed by rotary evaporation (30–40 °C, 20 mmHg). The resulting viscous, colorless, and cloudy oil (about 20 mL) is diluted with water (70 mL) and diethyl ether (50 mL). The mixture is stirred for 5 min and then the aqueous layer is separated and extracted with ether (3 x 50 mL). The combined ether layers are washed with saturated NaHCO_3 solution (50 mL) and saturated NaCl solution (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation (20 °C, 20 mmHg) to give 5.80 g of a colorless solid. This material is dissolved in boiling pentane (about 30 mL) in a 50-mL Erlenmeyer flask heated on a hot plate and the solution is cooled to 0 °C. The resulting solid is collected by vacuum filtration on a Büchner funnel, washed with ice-cold pentane (10 mL), and then dried at 20 mmHg to afford 5.57 g (86%) of 2,8-nonanedione as colorless crystals (Note 6).

2. Notes

1. 1,8-Nonadiyne (98% purity) was purchased by the submitters from Acros Organics and used as received. The checkers obtained the diyne (98% purity) from Aldrich Chemical Co.

2. Methyl(triphenylphosphine)gold(I) was prepared as follows according to the procedure of ref. 4. A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum, a reflux condenser fitted with an argon inlet, and a magnetic stirbar was evacuated and filled with argon. Chloro(triphenylphosphine)gold(I) (Strem Chemicals, 98+% purity) (0.5 g, 1.0 mmol, 1 equiv) and 6 mL of diethyl ether (purified by pressure filtration through activated alumina) were added and the resulting colorless suspension was cooled to 0 °C. Methylmagnesium iodide solution (3M in diethyl ether, Aldrich Chemical Co.) (1.7 mL, 5.1 mmol, 5.1 equiv) was added dropwise via syringe over 10 min. The resulting mixture was heated at reflux (oil bath temperature 50–55 °C) for 1 h and then allowed to cool to room temperature. Ice-cold 0.5% H₂SO₄ solution (24 mL, degassed by argon purging for 30 min before use) was added, resulting in the formation of a purple precipitate. Diethyl ether (3 mL, purified by pressure filtration through activated alumina) was added and the resulting mixture of two liquid phases and the precipitate was vacuum filtered through a Büchner funnel (washing with three 10-mL portions of toluene that had been purified by pressure filtration through activated alumina). The combined filtrates were transferred to a separatory funnel and the layers were separated. The organic phase was washed with 50 mL of water, dried over anhydrous Na₂SO₄, filtered, and concentrated to a volume of about 10 mL. This solution was transferred to a 50-mL Erlenmeyer flask, diluted with 30 mL of hexane (degassed by purging with argon for 30 min prior to use), and then slowly cooled to –18 °C. The resulting crystals were collected on a Büchner funnel by vacuum filtration (washing with ca. 15 mL of ice-cold hexane) and air-dried to give 0.248 g (52%) of methyl(triphenylphosphine)gold(I) as colorless crystals. The product exhibits the following physical properties: mp: 164–167 °C (lit.⁴ 167–168 °C); ¹H NMR (300 MHz, CDCl₃) δ: 0.55 (d, *J*_{PH} = 7.8 Hz, 3 H), 7.43–7.58 (m, 15 H); ³¹P NMR (121 MHz, CDCl₃) δ: 47.6; Anal. Calcd for C₁₉H₁₈AuP: C, 48.12; H, 3.83; Found: C, 48.11; H, 3.51.

3. Concentrated sulfuric acid was obtained by the checkers from Mallinckrodt Chemicals and was diluted with deionized water. The aqueous acid was degassed by purging with argon for 30 min prior to use.

4. Methanol was purchased by the submitters from Wako Pure Chemical Industries, Ltd. and used as received. The checkers obtained anhydrous methanol from Mallinckrodt Chemicals. The methanol was degassed by purging with argon for 30 min prior to use.

5. The submitters employed a Shimadzu GC-17A gas chromatograph equipped with a capillary column of Ultra Alloy UA1-30M-0.25F with a stationary phase of poly(dimethylsiloxane) using the following conditions: initial temperature at 50 °C, then increased at a rate of 10 °C/min, and held at 250 °C for 30 min. The checkers used a HP 6890 Series GC system equipped with a capillary column HP-5 with 5% phenyl dimethylpolysiloxane as the stationary phase under the following conditions: initial temperature 50 °C, then increased at a rate of 10 °C/min, and held at 240 °C for 30 min. Retention time of 1,8-nonadiyne: 4.37 min.

6. The product has the following characteristics: mp 47–48 °C (lit.⁵ 47–48 °C); ¹H NMR (500 MHz, CDCl₃) δ: 1.22–1.28 (m, 2 H), 1.54 (apparent quintet, *J* = 7.5 Hz, 4 H), 2.10 (s, 6 H), 2.40 (t, *J* = 7.5 Hz, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ: 23.6, 28.7, 30.1, 43.5, 209.1; IR (KBr): 2936, 2866, 1716, 1702, 1464, 1408, 1378, 1360, 1230, 1163, 958 cm⁻¹; Anal. Calcd for C₉H₁₆O₂: C, 69.19; H, 10.32. Found: C, 68.92; H, 10.56.


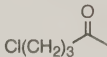
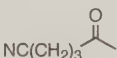





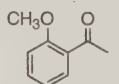
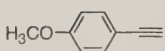
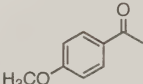
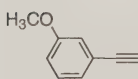
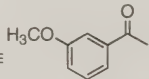
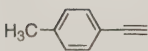
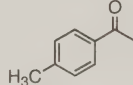


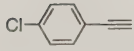
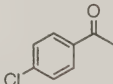


Safety and Waste Disposal Information

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3. Discussion

2,8-Nonanedione is a useful synthetic intermediate for the synthesis of rootworm sex pheromones, among other applications. The methods for the synthesis of 2,8-nonanedione have been recently summarized by Keinan and coworkers⁶ as follows: (1) mercury-catalyzed hydration of 1,8-nonadiyne,⁷ (2) palladium-catalyzed Wacker oxidation of 1,8-nonadiene,⁸ (3) reaction of 1,5-pentylene biscadmium halide with acetyl chloride,⁹ (4) oxidative cleavage of 2-methylcycloheptanone,⁵ and (5) reaction of bromohexanone ketal and acetoacetate.⁶ Other synthetic routes include (6) alkylation of acetone dimethylhydrazone followed by hydrolysis,¹⁰ (7) condensation of an alkoxyalkyl phenyl sulfone and a dihalopentane,¹¹ (8) imidazolylolation of pimelonamide followed by alkylation and elimination,¹² and (9) alkylation of a phosphonium salt of pimeloyl chloride followed by hydrolysis.¹³

Table 1 Preparation of Various Methyl Ketones^a

Alkyne	Product	[(PPh ₃)AuCH ₃]/mmol	Time	Yield ^b
$n\text{-C}_4\text{H}_9\text{—}\equiv$		0.002	2 h ^c	99%
$\text{Cl}(\text{CH}_2)_3\text{—}\equiv$		0.01	4 h ^d	72%
$\text{NC}(\text{CH}_2)_3\text{—}\equiv$		0.002	1 h	83%
		0.01	1 h	90%
		0.002 ^e	1 h	98%
		0.002	1 h	95%
		0.002	1 h	93%
		0.01	1 h	77%
		0.002 ^e	1 h	96%
		0.002	1 h	66%
		0.01	1 h	54%
		0.01	1h	92%

a) Catalyst [(Ph₃P)AuCH₃], alkyne 1 mmol, water 0.5 mL, H₂SO₄ 0.5 mmol, methanol 1-3 mL, 70 °C. b) Yields by GC c) 60 °C. d) Under CO atmosphere. e) CF₃SO₃H instead of H₂SO₄.

However, reactions (3) - (9) are multi-step procedures that give massive salt waste. Wacker oxidation (2) is principally the best reaction, while the oxidation of 1,8-nonadiene⁸ itself is not selective.

On the other hand, acid-catalyzed hydration of alkynes to give carbonyl compounds is one of the most straightforward methods to form the carbon-oxygen bond and is long known.¹⁴ However, only electron-rich alkynes react satisfactorily. The reaction of simple alkynes is sluggish and requires a co-catalyst such as mercury(II) salts^{6,15} as in reaction (1). To avoid the use of toxic mercury(II) salts, the use of various transition metal complexes such as Ru(II),¹⁶ Ru(III),¹⁷ Rh(III),¹⁸ Pt(II),¹⁹ and Au(III)²⁰ have been examined. However, the efficiencies of these catalyst systems have remained insufficient and the highest turnover frequency is in the 100/h range. Recently, Teles and coworkers²¹ have claimed in a patent application that hydration of propargyl alcohol is catalyzed by an Au(I)-acid catalyst system. However, the efficiency is still low.

We have discovered that simple alkynes can be hydrated by the CH₃AuPPh₃-acid catalyst system to give the corresponding methyl ketones in high yields.³ The reaction is significantly affected by the reaction media and methanol is the best solvent. Turnover frequency increases in methanol to 15600/h.²²

The reaction is applied not only to simple alkynes and diynes, but also to various alkynes as shown in Table 1. Aliphatic terminal alkynes give corresponding methyl ketones in good yields, even when electron withdrawing substituents such as chloro and cyano groups are attached. The use of CO atmosphere is required in some cases. Though C=C and C≡N groups can be potentially hydrated or hydrolyzed, both groups remain intact in the presence of this CH₃AuPPh₃-acid catalyst system. Aromatic alkynes give the corresponding acetophenones in high yields, while the use of CF₃SO₃H instead of H₂SO₄ is required in some cases. The presence of electronegative *o*- and *p*-chloro- and *m*-methoxy-substituents results in lower yields. The present catalyst CH₃AuPPh₃ is also applicable to hydroamination of alkynes.²³

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2. Present affiliation: Tokyo Institute of Technology.
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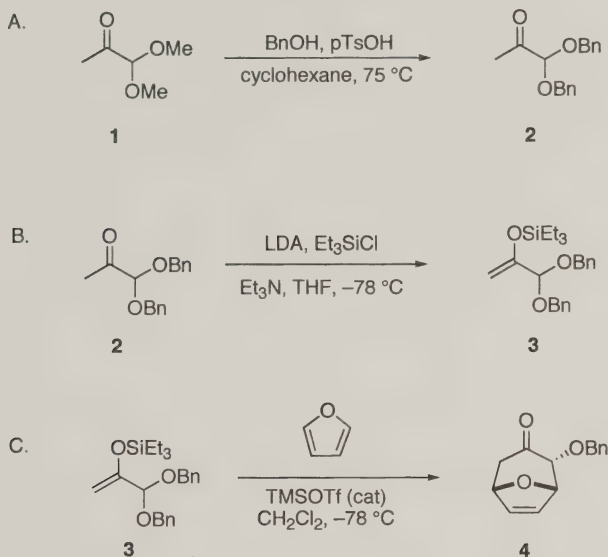
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21. Schulz, M.; Teles, J. H. U. S. Patent 6,037,482 for BASF, Mar. 14, 2000.
22. Reaction conditions: 1-octyne 20 mmol, CH₃AuPPh₃ 0.001 mmol, CF₃SO₃H 0.5 mmol, H₂O 1 mL, methanol 10 mL, 70°C, 1 h, under CO atmosphere.
23. Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.*, **2003**, *5*, 3349.

Appendix

Chemical Abstracts Nomenclature (Registry Number)

Methyl(triphenylphosphine)gold (CH₃AuPPh₃); (23108-72-7)
 1,8-Nonadiyne; (2396-65-8)
 2,8-Nonanedione; (30502-73-9)

SYNTHESIS OF 2 α -BENZYLOXY-8-OXABICYCLO[3.2.1]OCT-6-EN-3-ONE BY [4+3] CYCLOADDITION



Submitted by María Vidal-Pascual, Carolina Martínez-Lamenca and H. M. R. Hoffmann.¹

Checked by Timothy E. Long and Marvin J. Miller.

1. Procedure

A. *1,1-Bis(benzyloxy)propan-2-one* (**2**). A one-necked, 100-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with pyruvic aldehyde dimethyl acetal (12.1 mL, 100 mmol) in cyclohexane (50 mL), benzyl alcohol (22.8 mL, 220 mmol) and *p*-toluenesulfonic acid monohydrate (0.95 g, 5 mmol) (Note 1). The resulting mixture is heated at reflux for 2 h using a Dean–Stark separator for the removal of methanol. When the reaction is complete (approximately 2 h), approximately 8.1 mL (200 mmol) of MeOH is obtained. The reaction mixture is cooled to room temperature and washed with saturated potassium carbonate solution (25 mL) and water (20 mL). The aqueous layer is extracted twice with cyclohexane (2 x 50 mL). The combined organic phase is dried (Na₂SO₄), filtered, evaporated and the crude black oil is purified by column

chromatography using a 10-cm diameter column packed with 900 g silica gel (Note 2) and eluting with 2.1 L of MTBE/cyclohexane (1:20) to afford keto acetal **2** as a yellowish oil (22.3 g, 83%) (Note 3).

B. *[1,1-(Bis-benzyloxymethyl)vinyl]oxytriethylsilane* (**3**) (Note 4). An LDA solution is prepared in a 250-mL, two-necked, round-bottomed flask equipped with a nitrogen inlet and nitrogen balloon, magnetic stirring bar and rubber septum by adding BuLi (1.6 M solution in hexane, 22.5 mL, 36 mmol) (Note 5) into a solution containing diisopropylamine (5.1 mL, 36 mmol) (Note 6) in THF (36 mL) (Note 7) at -78°C (Note 8). The resulting mixture is stirred for an additional 15 min at room temperature. A separate two-necked, 250-mL round-bottomed flask is equipped with two septa and a nitrogen balloon. Dibenzyl acetal **2** (8.1 g, 30 mmol) and chlorotriethylsilane (7.5 mL, 45 mmol) (Note 9) are dissolved in THF (30 mL) under a nitrogen atmosphere. This mixture is cooled to -78°C and the LDA solution is added by cannula over the course of 10 min. Triethylamine (18.8 mL, 135 mmol) (Note 10) was immediately added by syringe over the course of 10 min. The resulting reaction mixture is stirred for 16 h at -78°C . Water (25 mL) is added, the cooling bath is removed, and the mixture is stirred until it reaches room temperature. The aqueous phase is extracted twice with cyclohexane. After being dried over sodium sulfate (Na_2SO_4) the organic solution is concentrated under vacuum and purified by column chromatography (6-cm diameter column, 360 g silica gel, MTBE/cyclohexane (1:100, 9 L) with 0.1% Et_3N) (Note 11) to give **3** as a yellow oil (8.9 g, 77%) (Notes 12, 13).

C. *2 α -Benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one* (**4**). A 250-mL, one-necked, round-bottomed flask capped with a rubber septum and equipped with a nitrogen balloon and magnetic stirring bar is charged under nitrogen atmosphere with silyl enol ether **3** (9.2 g, 24 mmol) (Note 14) and dichloromethane (25 mL) (Note 15). The mixture is cooled to -78°C , and furan (1.8 mL, 24 mmol) (Note 16) is added by syringe. After 15 min at -78°C , TMSOTf (0.46 mL, 2.4 mmol) is added by syringe (Note 17). The mixture is stirred for 30 min at -78°C and then a saturated solution of sodium bicarbonate (25 mL) is added. The cooling bath is removed and the flask is shaken thoroughly until the mixture reaches room temperature. The aqueous layer is extracted with dichloromethane (3×25 mL) and the combined organic phase is dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude product is purified by column chromatography (5-cm diameter column, 250 g silica gel, MTBE/cyclohexane (1:3)) giving cycloadduct **4** as a colorless oil (3.72 g,

70%) (Note 18). On storage in the freezer at $-25\text{ }^{\circ}\text{C}$, the product crystallizes from *tert*-butyl methyl ether to give a white solid (2.87 g, 54%) mp $64\text{--}65\text{ }^{\circ}\text{C}$ (Notes 19-20).

2. Notes

1. Pyruvic aldehyde dimethyl acetal was purchased from Acros Organics. Benzyl alcohol was purchased from Lancaster. *p*-Toluenesulfonic acid was purchased from Aldrich.

2. Silica gel (230-400 mesh) was obtained from Macherey Nagel.

3. Spectral data for 1,1-bis(benzyloxy)propan-2-one **2**: ^1H NMR (500 MHz, CDCl_3) δ : 2.33 (s, 3 H), 4.68 (d, $J = 12\text{ Hz}$, 2 H), 4.78 (d, $J = 12\text{ Hz}$, 2 H), 4.84 (s, 1 H), 7.41–7.45 (m, 10 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 25.0, 69.2, 101.0, 127.4, 128.0, 128.5, 137.0, 203.7. EI-MS (m/z): 271 (5), 259 (15), 228 (10), 182 (18), 181 (100), 165 (14); HRMS (FAB) (m/z): calcd for $\text{C}_{17}\text{H}_{19}\text{O}_2$ ($\text{M}^+ + 1$) 271.1334, observed 271.1308.

4. The preparation of [(1,1-bis(benzyloxy)methyl)vinyl]oxytriethylsilane (**3**) is appropriate for scales of 30 mmol of dibenzyl acetal or less. See Note 20 for information regarding larger scale reactions.

5. A commercial solution of 1.6 M butyllithium in hexane from Acros Organics was used.

6. Diisopropylamine was purchased from Acros and was distilled from KOH pellets and stored over solid KOH, purchased from Fisher Scientific.

7. Tetrahydrofuran supplied by Mallinckrodt is dried by distillation from sodium and benzophenone under an argon atmosphere.

8. The reaction mixture is cooled to $-78\text{ }^{\circ}\text{C}$ using dry ice-acetone bath or a cryostat.

9. Chlorotriethylsilane from both Acros Organics and Gelest, Inc. was used.

10. Triethylamine was dried and distilled from and stored over KOH pellets purchased from Fisher Scientific.

11. The checkers found that addition of triethylamine to the eluent is required to prevent decomposition of the silyl enol ether during chromatography.

12. Spectral data for [(1,1-bis(benzyloxy)methyl)vinyl]oxytriethylsilane **3**: ^1H NMR (300 MHz, CDCl_3) δ : 0.69 (q, $J = 7.8\text{ Hz}$, 6 H), 0.95 (t, $J = 8.1\text{ Hz}$, 9 H), 4.37 (d, $J = 1.2\text{ Hz}$, 1 H), 4.57 (d, $J = 12\text{ Hz}$, 2 H); 4.63 (d, $J = 11.7\text{ Hz}$, 2 H), 4.70 (s, 1 H), 4.89 (s, 1 H), 7.31–7.26 (m,

10 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 4.9, 6.7, 67.6, 92.3, 99.2, 127.5, 127.8, 128.4, 138.2, 153.8. EI-MS (m/z): no M^+ , 279 (9), 249 (4), 248 (3), 193 (4), 187 (6), 181 (7), 159 (14), 157 (13), 115 (17), 91 (100).

13. The submitters report that this procedure can also be used for the preparation of 3,3-bis-benzyloxy-2-trimethylsilyloxypropene by using chlorotrimethylsilane (from Acros Organics) instead of chlorotriethylsilane. In that case, the resultant trimethylsilyl enol ether cannot be purified by column chromatography due to its acid sensitivity, so the crude product is used directly in the [4+3] cycloaddition reaction (Note 20).

14. An alternative to silyl enol ether **3** as oxyallylic cation precursor is 3,3-bis-benzyloxy-2-trimethylsilyloxypropene (Notes 13, 20).

15. Commercial dichloromethane was freshly distilled from CaH_2 .

16. Commercial furan (99%, stabilized with BHT) from Acros Organics was used without further purification. 2,5-Dimethylfuran (99%) from Acros Organics was used by the submitters in the unchecked [4+3] cycloaddition (85% yield of cycloadduct) following the same procedure as for furan.

17. Commercial trimethylsilyl trifluoromethanesulfonate (99%) from Acros Organics was used. Ten mole % (0.1 equiv) of TMSOTf was sufficient to catalyze the [4+3] cycloaddition.

18. The checkers observed that the oil partially solidifies to a white solid upon standing. The submitters report that residual benzyl alcohol can be removed by heating the oil at 100 °C for two hours using a Kugelrohr apparatus. The checkers did not identify the presence of benzyl alcohol by NMR analysis and did not perform the heating.

19. Spectral data for 2 α -benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one **4**: ^1H NMR (500 MHz, CDCl_3) δ : 2.37 (d, J = 15.5 Hz, 1 H), 2.75 (dd, J = 15, 5 Hz, 1 H), 4.13 (d, J = 5 Hz, 1 H), 4.64 (d, J = 12 Hz, 1 H), 4.91 (dd, J = 5, 1.5 Hz, 1 H), 4.99 (m, 2 H), 6.30 (dd, J = 6.5, 1.5 Hz, 1 H), 6.34 (dd, J = 6, 2 Hz, 1 H), 7.39–7.31 (m, 5 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 46.1, 73.7, 78.6, 80.0, 84.3, 128.1, 128.7, 132.0, 134.8, 137.8, 205.2. IR (CHCl_3) cm^{-1} : 1724 (very strong), 1112 (very strong), 731 (strong), 697 (strong); EI-MS (rt): 230 (6, M^+), 201 (4), 158 (38), 139 (31, $\text{M}^+ - \text{Bn}$), 121 (10), 108 (25), 91 (100), 81 (30), 77 (14), 69 (23). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$: C, 72.89; H, 6.05. Found: C, 73.03; H, 6.13.

20. Alternatively, the [4+3] cycloadduct has been prepared by the submitters using inexpensive chlorotrimethylsilane (Note 13) as follows:

A two-necked, 250-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with dibenzyl acetal **2** (27 g, 100 mmol) in

anhydrous DMF (33 mL) (Dimethylformamide (DMF) is dried over powdered BaO for 2 weeks, followed by decanting and then distilling under reduced pressure.) and chlorotrimethylsilane (28.6 mL, 225 mmol) (Note 13) and heated at 75 °C. Triethylamine (38.9 mL, 280 mmol) (Note 10) is added slowly by syringe pump (60 mL/h). The reaction mixture is refluxed for 16 h at 75 °C and the reaction mixture becomes thicker and dark brown. The reaction mixture is cooled to 0 °C, washed with 30 mL of a cold saturated solution of ammonium chloride (30 mL) and water (approximately 15 mL). The aqueous phase is extracted with cyclohexane (4 x 50 mL). The combined organic phase is dried (Na₂SO₄) and the solvent removed with a rotatory evaporator. The resulting brown viscous oil is used directly in the [4+3] cycloaddition as described in procedure C.

When the 3,3-*bis*-benzyloxy-2-trimethylsilyloxypropene is used as the oxyallylic cation precursor, the yield of the [4+3] cycloadduct with furan is 41 % (two steps). The yield of the [4+3] cycloadduct with 2,5-dimethylfuran is 53 % (two steps). The procedure has been used in a reaction using 130-mmol of starting dibenzyl acetal.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

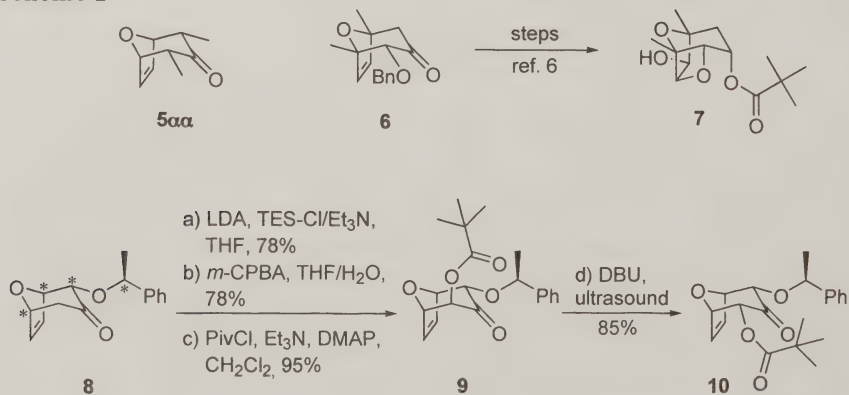
3. Discussion

In view of the wide synthetic interest of [4+3] cycloadducts of oxyallyl cations and dienes, a variety of methods have been developed for the generation and capture of appropriate oxyallyl cations. The classical routes to generate these reactive intermediates start from halogenated precursors:² α,α' -Dihalo ketones or α -monohalo ketones. For example, 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (5 α,α) has been prepared from both a dihalo-^{3a} and a monohaloketone^{3b} and has served as a *meso*-configured workhorse for exploring desymmetrization of the seven-carbon backbone with its three pro-stereogenic sp² centers. Allylic halides and silver salts have been used also.^{2a, 4} Further, the use of trialkylsilyloxyallyl cations from 1,1-dimethoxyacetone in [4+3] cycloadditions with furans has been reported.⁵

In the procedure described here, a triethylsilyloxyallylic cation with a π -donating benzyloxy substituent at the allylic terminus is generated via treatment of triethylsilyl enol ether **3** with TMSOTf in catalytic amount and, in presence of the 4π -component, the [4+3] cycloaddition proceeds smoothly giving 2 α -benzyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-ones. If furan is replaced by 2,5-dimethylfuran, then cycloaddition yields are higher (leading to **6**). Increasing the equivalents of diene does not alter the yield appreciably. The availability of oxabicyclic **6** opens a short route to the dioxatricyclic core of the marine metabolite dictyoxetane (**6** \rightarrow **7**)^{6a} and to functionalized scopolines.^{6b} An asymmetric variant of the [4+3] cycloaddition involving chiral allyl cations has also been accomplished affording **8** with high *ee*.⁷

Oxabicyclic **8** is a useful building block and is endowed with all the chiral information for the *de novo* construction of C-glycosides. For example, axial hydroxylation (**8** \rightarrow **9**) proceeds smoothly by treatment of the derived TES enol ether with *m*-chloroperbenzoic acid provided that *wet* THF is used as solvent.⁸ The use of dilute solutions of dimethyldioxirane as oxidant which is toxic and dangerous, is obviated.⁹ Epimerization of **9** affords the diequatorial epimer **10**. Starting from **8** and parent 8-oxabicyclo[3.2.1]oct-6-en-3-one, a complete series of C-glycosides with fully resolved seven-carbon backbone polyol stereochemistry and with complete anomeric control has been prepared (Scheme 1).⁸

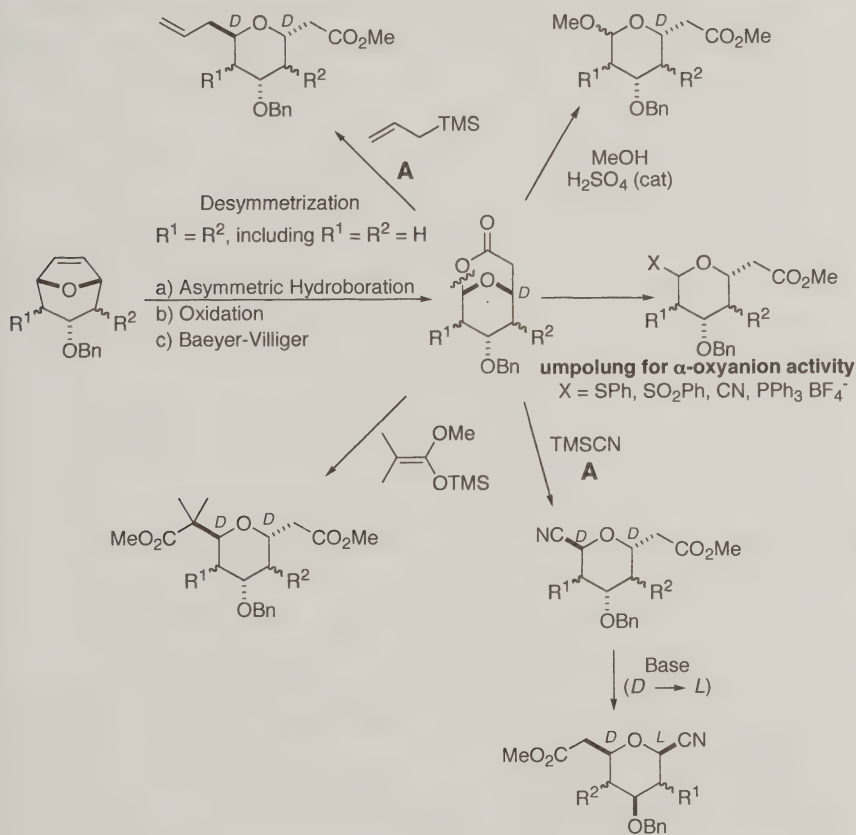
Scheme 1



8-Oxabicyclo[3.2.1]oct-6-en-3-ones have been converted into [3.3.1]lactone acetals, which are versatile synthetic intermediates and allow further stereocontrolled C–C, C–S, C–P⁺Ph₃X[–] bond formation. C–C Bonds and extended carbon chains are formed with complete anomeric control in

the presence of a Lewis acid (Me_3SiOTf) and silylated nucleophile in acetonitrile (Scheme 2).¹⁰ 8-Oxabicyclo[3.2.1]oct-6-en-3-ones have been used as key precursors in natural product syntheses, as accomplished by the total synthesis of hinokitiol¹¹ and callistatin A.¹²

Intramolecular [4+3] cycloadditions have also been studied.¹³ Recently, metathesis of substituted oxabicyclics combined with spiroannulation has been reported.¹⁴ Ru-Catalyzed asymmetric ring-opening/cross-metathesis provides another efficient enantioselective route to functionalized tetrahydropyrans.¹⁵ Vinylic nonaflates from 8-oxabicyclo[3.2.1]oct-6-en-3-ones have been used to elaborate the bicyclic scaffold.¹⁶



Scheme 2. Typical transformations of [3.3.1]lactone acetals illustrated for C-glycoside synthesis with generalized *D-D* type configuration. **A:** All reactions were run with TMSOTf (ca. 1 equiv) in MeCN , $-40\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$; then addition of MeOH , r.t. followed by *in situ* esterification. Yields are uniformly about 95%.

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Appendix

Chemical Abstracts Nomenclature; (Registry number)

1,1-Dimethoxy-2-propanone: α,α -Dimethoxyacetone; (6342-56-9)

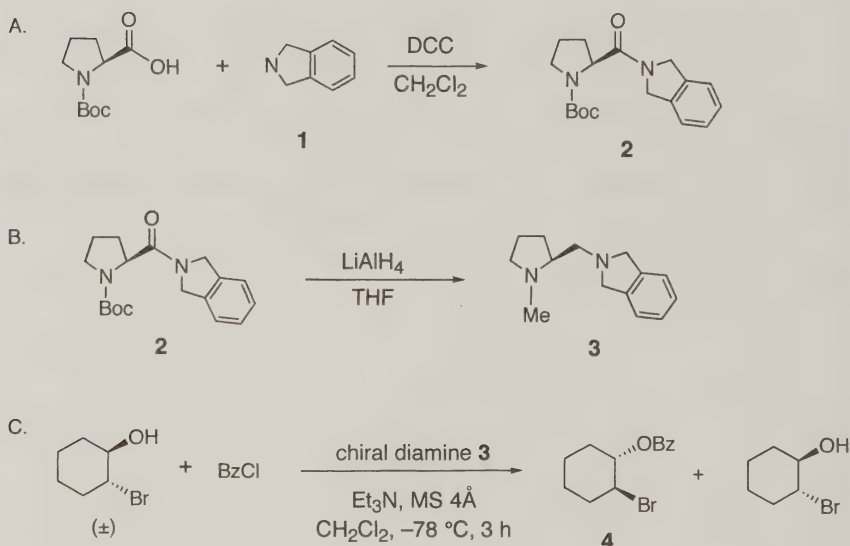
Chlorotriethylsilane: Silane, chlorotriethyl-; (994-30-9)

Trimethylsilyl trifluoromethanesulfonate: Trifluoromethanesulfonic acid trimethylsilyl ester; Trimethylsilyl triflate; (27607-77-8)

Chlorotrimethylsilane: Silane, chlorotrimethyl-; (75-77-4)

2,5-Dimethylfuran; (625-86-5)

**CATALYTIC ASYMMETRIC ACYLATION OF ALCOHOLS USING
A CHIRAL 1,2-DIAMINE DERIVED FROM (S)-PROLINE:
(1S,2S)-trans-1-BENZOYLOXY-2-BROMOCYCLOHEXANE**



Submitted by Dai Terakado and Takeshi Oriyama.¹

Checked by Jing Zhang, Fangzheng Li and Marvin J. Miller.

1. Procedure

A. *(S)*-*N*-(*N*-*tert*-Butoxycarbonylprolyl)dihydroisoindole (**2**). A dry, 100-mL, two-necked flask equipped with a Teflon-coated magnetic stirring bar and a septum cap is charged with (*S*)-*N*-*tert*-butoxycarbonylproline (5.05 g, 23.5 mmol) (Note 1), dihydroisoindole (2.54 g, 21.3 mmol) (Note 2), and dichloromethane (25 mL) (Note 3) under an argon atmosphere. After cooling to 0 °C with the aid of an ice-water bath, a solution of dicyclohexylcarbodiimide (DCC, 5.1 g, 24.7 mmol) (Note 4) in dichloromethane (20 mL) (Note 3) is added and the reaction mixture is allowed to warm to room temperature while stirring overnight. The mixture is filtered through Celite, concentrated, and purified by column chromatography (Note 5) (ethyl acetate/hexanes:1/3) to afford

(*S*)-*N*-(*N*-*tert*-butoxycarbonylpropyl)dihydroisoindole (4.1 g, 61%) as a white solid (Note 6).

B. (*S*)-1-Methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (**3**). A dry, 200-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a reflux condenser, a septum cap, and an argon inlet is charged with lithium aluminum hydride (LAH, 0.96 g, 25.3 mmol) in THF (10 mL). After cooling to 0 °C with the aid of an ice-water bath, a solution of (*S*)-*N*-(*N*-*tert*-butoxycarbonylpropyl)dihydroisoindole (3.96 g, 12.5 mmol) in THF (15 mL) was added under an argon atmosphere. The cooling bath is removed and the reaction mixture is refluxed for 3 h. After cooling the mixture to 0 °C, the reaction is quenched carefully by the slow addition of saturated aqueous sodium sulfate (approx 5 mL). The liquid is decanted away from the precipitate, and the precipitate was washed with THF (2 x 20 mL). The combined liquid is dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (CH₂Cl₂/MeOH/Et₃N:95/5/1), to afford (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (**3**) (1.56 g, 58%) (Note 7).

C. (1*S*,2*S*)-*trans*-1-Benzoyloxy-2-bromocyclohexane (**4**). A 100-mL, two-necked flask equipped with a Teflon-coated magnetic stirring bar and a septum cap is charged with 1 g of molecular sieves 4 Å (Note 8), and flame-dried under reduced pressure. After being allowed to warm to ambient temperature, the apparatus is flushed with argon. The flask is charged with (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (65 mg, 0.28 mmol) in dichloromethane (5 mL) (Note 3), triethylamine (5.56 g, 55 mmol) (Note 9) in dichloromethane (15 mL), and racemic *trans*-2-bromocyclohexanol (17.91 g, 100 mmol) (Note 10) in dichloromethane (40 mL) by means of an oven-dried syringe and needle. After cooling to -78 °C by immersion in a dry-ice bath, benzoyl chloride (9.14 g, 65 mmol) (Note 11) in dichloromethane (20 mL) is added slowly over 30 min by means of an oven-dried syringe and needle. The solution is stirred for 3 h at -78 °C, and then quenched with a phosphate buffer (pH 7) (Note 12). The layers are separated and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic phase is washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under

vacuum. The crude products are purified by column chromatography (Note 13) (ethyl acetate/hexanes:1/50) to give (1*S*, 2*S*)-*trans*-1-benzoyloxy-2-bromocyclohexane (14.25 g, 50%) (Note 14) and unreacted alcohol (1*R*, 2*R*)-*trans*-2-bromocyclohexanol (6.60 g, 37%) (Note 15).

2. Notes

1. The checkers purchased (*S*)-*N*-*tert*-butoxycarbonylproline from Aldrich Chemical Company.

2. The checkers purchased dihydroisoindole (isoindoline) from Aldrich Chemical Company.

3. Dichloromethane was purchased by the submitters as anhydrous solvent from Kanto Chemical Company, Inc., and used without further purification. The dichloromethane used by the checkers was purchased from Fisher Scientific and distilled from CaH₂ prior to use.

4. Dicyclohexylcarbodiimide (DCC) used by the submitters was purchased from Tokyo Kasei Kogyo Co. The checkers used DCC purchased from Aldrich Chemical Co. The submitters reversed the addition by adding the substrates to the DCC mixture. However, the checkers found that the substrates were incompletely soluble in methylene chloride and that transfer was then incomplete.

5. Column chromatography was performed (38 mm x 600 mm column) on Wakogel C-200 that purchased from Wako Chemical Company, Inc. The checkers used Merck silica gel with a 45 mm x 200 mm column.

6. The submitters reported 100% yield. The analytical and spectral data of (*S*)-*N*-(*N*-*tert*-butoxycarbonylpropyl)dihydroisoindole are as follows: mp 150–152 °C (decompose), $[\alpha]_D^{24}$ –18.4 (*c* 1.0, EtOH). The checkers obtained $[\alpha]_D$ –19.8 (*c* 1.0, EtOH); The NMR spectra show the presence of two rotameric forms in an approximate 1:1 ratio. Resonances for both rotamers are included in the following characterization data. ¹H NMR (300 MHz, CDCl₃) δ: 1.35 (s, 9 H), 1.46 (s, 9 H), 1.82–2.02 (m, 4 H), 2.08–2.29 (m, 4 H), 3.42–3.68 (m, 4 H), 4.47 (dd, 1 H, *J* = 8.1, 4.8 Hz), 4.59 (dd, 1 H, *J* = 7.7, 3.3 Hz), 4.72–4.91 (m, 6 H), 4.99 (d, 1 H, *J* = 13.6 Hz), 5.18 (d, 1 H, *J* = 13.6 Hz), 7.22–7.32 (m, 8 H); ¹³C NMR (75 MHz, CDCl₃) δ: 23.94 (CH₂), 24.55 (CH₂), 28.50 (CH₃), 28.63 (CH₃), 29.64 (CH₂), 30.49 (CH₂), 46.82 (CH₂), 47.03 (CH₂), 52.35 (CH₂), 52.46 (CH₂), 52.56 (CH₂), 57.55 (CH), 57.89 (CH), 79.69 (C), 79.77 (C), 122.70 (CH), 122.75 (CH), 123.02 (CH), 123.20 (CH), 127.53 (CH), 127.73 (CH), 127.83 (CH), 128.07 (CH), 136.13 (C), 136.26 (C), 136.42 (C), 136.50 (C), 153.92 (C), 154.71 (C),

171.73 (C), 171.89 (C); IR (neat) cm^{-1} : 2967, 2867, 1694, 1653, 1405, 1358, 1163, 1127, 888, 755; MS (FAB) exact mass, (m/z) Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_3$ 317.1865, Found 317.1862; Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.16; H, 7.60; N, 8.65.

7. The submitters reported 60% yield after distillation under reduced pressure. The checkers had difficulty with reproducibility using distillation. The yield obtained by the checkers after chromatography varied between 58% and 65%. The checkers used Merck silica gel with a 45 mm x 200 mm column. The analytical and spectral data of (*S*)-1-methyl-2-[(dihydroisoinol-2-yl)methyl]pyrrolidine are as follows: bp 112–114 °C / 0.6 mmHg, $[\alpha]_{\text{D}}^{24} -70.4$ (c 1.1, EtOH), ^1H NMR (300 MHz, CDCl_3) δ : 1.58–1.84 (m, 3 H), 1.94–2.06 (m, 1 H), 2.16 (dt, 1 H, $J = 9.6, 7.8$ Hz), 2.30 (m, 1 H), 2.40 (s, 3 H), 2.62 (dd, 1 H, $J = 11.7, 7.8$ Hz), 2.88 (dd, 1 H, $J = 12, 4.8$ Hz), 3.03 (m, 1 H), 3.89 (s, 4 H), 7.11 (s, 4 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 22.60 (CH_2), 30.53 (CH_2), 41.35 (CH_3), 57.67 (CH_2), 59.96 (CH_2), 60.94 (CH_2), 64.96 (CH), 122.04 (CH), 126.50 (CH), 140.28 (C); IR (neat) cm^{-1} : 2938, 2771, 1463, 1149, 742; MS (FAB) exact mass (m/z) Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2$ 217.1705, Found 217.1701. Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2$: C, 77.72; H, 9.32; N, 12.95. Found: C, 77.34; H, 9.53; N, 12.83.

8. Molecular sieves 4Å were purchased from Wako Chemical Company, Inc., and dried at 100 °C for 3 h as a powder under reduced pressure before use. The checkers used molecular sieves purchased from Aldrich Chemical Company.

9. Triethylamine was purchased from Tokyo Kasei Kogyo Co., and distilled before use. The triethylamine used by the checkers was purchased from Aldrich Chemical Company and was distilled from CaH_2 prior to use.

10. *trans*-2-Bromocyclohexanol was prepared from cyclohexene oxide and hydrobromic acid according to the following procedure: A 200-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with hydrobromic acid (47%, 40 mL, 346 mmol) and cooled at 0 °C by immersion in an ice-water bath. Cyclohexene oxide (20 mL, 198 mmol) is added dropwise and the mixture is stirred at room temperature for 8 h. After being cooled to 0 °C, the solution is neutralized by addition of saturated aqueous Na_2CO_3 (approx 30 mL) (*Caution: slow addition of the Na_2CO_3 solution is recommended due to excessive bubbling of the solution*), and extracted with diethyl ether (3 x 30 mL). The combined organic phases are dried over anhydrous sodium sulfate, filtered, concentrated, and distilled under reduced pressure to give *trans*-2-bromocyclohexanol (30.0 g, 85%) (bp 92 °C / 11 mmHg).

11. BzCl was purchased from Tokyo Kasei Kogyo Co., and distilled before use.

12. The buffer was prepared by dissolving 33.4 g of disodium hydrogenphosphate dodecahydrate and 6.4 g of potassium dihydrogenphosphate into 300 mL of water. The buffer solution was diluted to a final volume of 700 mL and stored in a glass bottle.

13. The checkers used Merck silica gel with a 70 mm x 200 mm column.

14. The checkers obtained 13.65 g (48%) of the benzoate (**4**) and 7.59 g (42%) of the alcohol. The submitters determined the enantiomeric excess of the benzoate (95% *ee*) by HPLC analysis using a Daicel CHIRALCEL OD column (*i*-PrOH:hexanes = 1:1000, 1.0 mL/min, 254 nm). The retention times for the (1*S*,2*S*)-*trans*-1-benzoyloxy-2-bromocyclohexane are 14.6 min ((+)-1*S*,2*S*) and 16.7 min ((-)-1*R*,2*R*). The checkers determined the enantiomeric excess of the benzoate to be 90% using a 25 x 0.46 cm Daicel CHIRALPAK AD-H column (*i*-PrOH:hexanes = 1:9, 1.0 mL/min, 254 nm). The retention times are 5.05 and 5.31 min. The analytical and spectral data of pure (1*S*, 2*S*)-*trans*-1-benzoyloxy-2-bromocyclohexane are as follows: $[\alpha]_D^{24} +104.6$ (*c* 1.0, CHCl₃, 90.0% *ee*); ¹H NMR (500 MHz, CDCl₃) δ : 1.35–1.44 (m, 1 H), 1.48–1.57 (m, 2 H), 1.75–1.85 (m, 2 H), 1.91–1.99 (m, 1 H), 2.25–2.33 (m, 1 H), 2.39–2.45 (m, 1 H), 4.16 (m, 1 H), 5.14 (dt, 1 H, *J* = 9.0, 4.5 Hz), 7.46 (t, 2 H, *J* = 7.5 Hz), 7.57 (m, 1 H), 8.07 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ : 23.5 (CH₂), 25.6 (CH₂), 31.3 (CH₂), 35.7 (CH₂), 52.8 (CH), 76.5 (CH), 128.5 (CH), 129.9 (CH), 130.4 (C), 133.2 (CH), 165.8 (C); IR (neat) cm⁻¹: 2941, 1720, 1450, 1274, 1104, 1027, 945, 711; MS (FAB) exact mass (*m/z*) Calcd for C₁₃H₁₅BrO₂ 283.0334, Found 283.0308. The submitters report that the product gave the following elemental analysis: Anal. Calcd for C₁₃H₁₅BrO₂: C, 55.14; H, 5.34. Found: C, 55.05; H, 5.42.

15. The enantiomeric excess was determined by the submitters to be >99% by HPLC analysis using Daicel CHIRALCEL OD (*i*-PrOH:hexanes = 1:1000, 1.0 mL/min, 254 nm) after conversion to the corresponding benzoate. The retention times for the (1*R*, 2*R*)-*trans*-1-benzoyloxy-2-bromocyclohexane are 14.3 min ((+)-1*S*,2*S*) and 16.8 min ((-)-1*R*,2*R*). The analytical and spectral data of (1*R*, 2*R*)-*trans*-2-bromocyclohexanol are as follows: $[\alpha]_D^{24} -33.0$ (*c* 1.0, CHCl₃, 99.3% *ee*); ¹H NMR (500 MHz, CDCl₃) δ : 1.22–1.40 (m, 3 H), 1.65–1.70 (m, 1 H), 1.77–1.86 (m, 2 H), 2.10–2.16 (m, 1 H), 2.30–2.36 (m, 1 H), 2.62 (brs, 1 H), 3.60 (dt, 1 H, *J* = 9.9, 4.5 Hz), 3.89 (ddd, 1 H, *J* = 12.1, 9.5, 4.5 Hz); ¹³C NMR (125 MHz,

CDCl₃) δ : 24.26 (CH₂), 26.8 (CH₂), 33.7 (CH₂), 36.4 (CH₂), 61.96 (CH), 75.4 (CH); IR (neat) cm⁻¹: 3350, 2835, 1450, 1070, 955.

Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

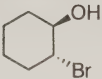
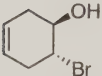
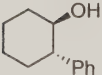

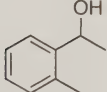
Asymmetric acylation of alcohols is divided into two types of reactions. These are kinetic resolution of racemic alcohols and desymmetrization of meso-polyols. Although most methods reported so far employ an enzyme such as a lipase or an esterase,² some outstanding asymmetric acylations of alcohols by using organocatalysts³ have recently emerged as reliable alternatives to the well established enzyme-catalyzed reactions.

Kinetic resolution of racemic alcohols via asymmetric acylation has been widely used to construct various useful chiral building blocks in the synthesis of complex natural products.⁴ The submitters have demonstrated highly enantioselective desymmetrization of *meso*-diols⁵ and highly efficient kinetic resolution of racemic secondary alcohols⁶ catalyzed by a chiral 1,2-diamine derived from (*S*)-proline.

Chiral diamine catalysts can be readily prepared in three steps from (*S*)-proline. This type of a 1,2-diamine is frequently used in important and fundamental asymmetric syntheses.⁷ This diamine has an advantage in that the non-proline amine portion can be easily modified to include, for example, cyclic pyrrolidine, piperidine, indoline skeletons, or the acyclic benzylmethylamino skeleton. More efficient reactions and higher enantioselectivities during asymmetric acylation of alcohols are achieved by using a chiral diamine containing a dihydroisoindole or a benzylmethylamino component. Representative results of asymmetric acylation of alcohols catalyzed by chiral 1,2-diamines are shown in Tables I and II.

TABLE I

CHIRAL 1,2-DIAMINE CATALYZED KINETIC RESOLUTIONS OF RACEMIC SECONDARY ALCOHOLS^a

Entry	Alcohol	Amine	Ester Yield ^b / %	ee ^c / %	Unreacted alcohol Yield ^b / %	ee ^d / %	<i>S</i> ^e
1		<i>i</i> -Pr ₂ NEt	47	96	39	95	130
2		<i>i</i> -Pr ₂ NEt	46	97	43	91	170
3		Et ₃ N	49	96	48	95	160
4 ^f		Et ₃ N	44	95	47	79	88
5		Et ₃ N	45	82	49	78	20

a) Reaction conditions : MS 4 Å (40 mg), (*S*)-1-methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (0.9 μmol), amine (0.15 mmol), alcohol (0.3 mmol), BzCl (0.23 mmol), -78 °C, 3 h. b) Isolated yield of purified product. c) Determined by chiral HPLC analysis. d) Determined by chiral HPLC analysis after conversion to corresponding benzoate. e) Selectivity factor, calculated from the conversion (isolated yield) and ee of the acylated product. f) Reaction was performed for 24 h.

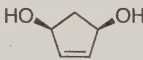


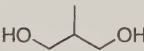
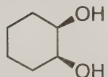
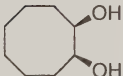
(1*S*,2*S*)-*trans*-1-Benzoyloxy-2-bromocyclohexane is a valuable synthetic precursor for allylic alcohol derivatives. An enantio-enriched allylic benzoate can be provided via β-elimination. Treatment of **4** with DBN (1,5-diazabicyclo[4.3.0]non-5-ene) in refluxing toluene gives the corresponding allylic benzoate, (*S*)-1-benzoyloxy-2-cyclohexene, without loss of enantio-purity.^{6c}

We have presented a promising small organocatalyst for asymmetric acylation of various alcohols including racemic secondary alcohols and *meso*-1,2-, 1,3-, and 1,4-diols. Catalytic asymmetric acylation of alcohols

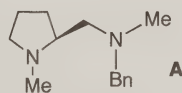
by using a chiral 1,2-diamine has the following distinguishing synthetic features: 1) high enantioselectivity, 2) high efficiency, 3) operational simplicity, 4) widespread applicability, and 5) the absence of a metal.

TABLE II

CHIRAL 1,2-DIAMINE CATALYZED ASYMMETRIC
DESYMMETRIZATION OF *meso*-DIOLS^a

Entry	<i>meso</i> -Diol	Amine	Solvent	Monoester Yield ^b / %	ee ^c / %
1 ^d		Et ₃ N	PrCN	38	98
2 ^{d,e}		Et ₃ N	PrCN	87	>99
3 ^f		<i>i</i> -Pr ₂ NEt	CH ₂ Cl ₂ - DMF (9 : 1)	57	>99
4		<i>i</i> -Pr ₂ NEt	PrCN	33	96
5 ^{g,h}		Et ₃ N	CH ₂ Cl ₂	92	98
6 ^{g,h}		Et ₃ N	CH ₂ Cl ₂	92	99

a) Reaction conditions : MS 4Å (40 mg), chiral 1,2-diamine (0.0015 mmol), amine (0.45 mmol), diol (0.3 mmol), *p*-*t*-BuC₆H₄COCl (0.45 mmol), -78 °C, 3 h. b) Isolated yield of purified product. c) Determined by chiral HPLC analysis. d) 0.51 mmol of BzCl and Et₃N were used. e) Reaction was performed for 8 h. f) Chiral 1,2-diamine **A** was used. g) 0.003 mmol of chiral 1,2-diamine and 0.3 mmol of Et₃N were used and silylation of monoalcohol was performed in one-pot after acylation for 3 h. h) *p*-CH₃C₆H₄COCl was used instead of *p*-*t*-BuC₆H₄COCl.



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

Di-*tert*-butyl dicarbonate: Formic acid, oxydi-, di-*tert*-butyl ester;
 Dicarmonic acid, bis(1,1-dimethylethyl)ester; (24424-99-5)
tert-Butoxycarbonyl-L-proline: 1,2-Pyrrolidinedicarboxylic acid,

1-(1,1-dimethylethyl)ester, (*S*)-*tert*-Butoxycarbonyl-L-proline
(15761-39-4)

Isoindoline, 1,3-Dihydroisoindole: 1*H*-Isoindole, 2,3-dihydro-; (496-12-8)

Dicyclohexylcarbodiimide: Carbodiimide, dicyclohexyl-; Cyclohexanamine,
N,N'-methanetetraylbis-; (538-75-0)

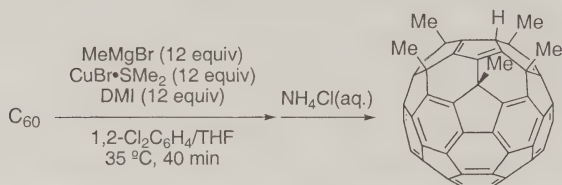
(*S*)-*N*-(*N-tert*-Butoxycarbonylpropyl)dihydroisoindole (188122-39-6)

(*S*)-1-Methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (159497-37-7)

trans-2-Bromocyclohexanol; (2425-33-4)

(1*S*, 2*S*)-1-Benzoyloxy-2-bromocyclohexane; Cyclohexanol, 2-bromo-,
benzoate, (1*S*,2*S*)-; (222851-77-6)

SYNTHESIS OF 6,9,12,15,18-PENTAMETHYL-1,6,9,12,15,18- -HEXAHYDRO(C₆₀-I_h)[5,6]FULLERENE



Submitted by Yutaka Matsuo, Ayako Muramatsu, Kazukuni Tahara, Madoka Koide, and Eiichi Nakamura.¹

Checked by Peter Wipf and David L. Waller.²

1. Procedure

A 200-mL two-necked, round-bottomed flask (Note 1) connected to a vacuum/nitrogen manifold through a three-way stopcock is equipped with a Teflon-coated magnetic stirring bar, a vacuum/nitrogen inlet, and a glass stopper. A microcrystalline sample of [60]fullerene (2.00 g, 2.78 mmol) (Note 2) is placed in the 200-mL flask and the apparatus is flushed with nitrogen. The glass stopper is replaced with a rubber septum, and 1,2-dichlorobenzene (90 mL) (Note 3) is introduced into the flask via a syringe under nitrogen. The rubber septum is again replaced with a glass stopper. The reaction mixture is cooled with an ice/water bath and stirred under reduced pressure (1 mmHg) for 30 min to remove dissolved oxygen. Then the flask is flushed with nitrogen and warmed to room temperature (approximately 23 °C).

A 500-mL three-necked, round-bottomed flask (Note 1), connected to a vacuum/nitrogen manifold through a three-way stopcock, is equipped with a 3-cm Teflon-coated magnetic stir bar, a vacuum/nitrogen inlet, a 100-mL pressure-equalizing dropping funnel with a glass stopper, and a glass stopper. The flask is charged with copper(I) bromide-dimethyl sulfide complex (6.84 g, 33.3 mmol) (Note 4) and flushed with nitrogen (Note 5). The glass stopper on the top of the pressure-equalizing dropping funnel is replaced with a rubber septum, and the 1,2-dichlorobenzene solution of [60]fullerene is transferred to the dropping funnel via a Teflon cannula. The glass stopper on the 500-mL flask is replaced with a rubber septum and tetrahydrofuran (47 mL) (Note 6) is added to the copper complex via syringe. The resulting white suspension is stirred and the flask is placed into an oil

bath (approximately 23 °C). A tetrahydrofuran solution of methylmagnesium bromide (3 M, 11.1 mL, 33.3 mmol) (Note 7) is added to this white suspension by syringe, followed by 1,3-dimethyl-2-imidazolidinone (DMI, 3.62 mL, 33.3 mmol) (Note 8). The organocopper reagent is quickly warmed in an oil bath to 35 °C within 5 min. The 1,2-dichlorobenzene solution of [60]fullerene in the dropping funnel is added at once to the organocopper reagent (Note 9). The color of the suspension changes to dark brown. The dropping funnel is replaced with a glass stopper.

After stirring for 40 min at 35 °C (Note 10), 3.0 mL of degassed saturated aqueous ammonium chloride solution is added quickly via syringe. The color of the mixture turns from dark brown to reddish brown. The septum is replaced with a glass stopper and the reaction mixture is stirred under reduced pressure (1 mmHg) at 23 °C to remove tetrahydrofuran and dimethyl sulfide until the volume is halved.

The concentrated mixture is diluted with degassed toluene (200 mL) and filtered through a pad of silica gel (Note 11) with toluene as eluent (Notes 12 and 13). The vermilion filtrate is collected into a 1-L, round-bottomed flask and concentrated on a rotary evaporator under reduced pressure (10 mmHg) at 40 °C. To remove 1,2-dichlorobenzene the bath temperature is raised to 80 °C until solid just begins to appear on the inside wall of the flask (Note 14). Nitrogen is added while the vacuum is broken, and the flask is removed from the rotary evaporator. Degassed methanol is added gently against the inside wall of the flask (Note 15). As methanol mixes with the product, the solution becomes cloudy and a precipitate forms. The addition is continued until precipitation is complete. The total amount of methanol required is approximately 400 mL. The precipitate is collected by filtration on a Buchner funnel (Note 16) and washed with methanol (5 x 10 mL) and hexane (3 x 10 mL). The product is dried under reduced pressure (1 mmHg) for 12 h at room temperature to obtain red microcrystals of the title compound (2.08 g, 2.61 mmol) in 94% overall yield and 91% purity (determined by HPLC analysis) (Note 17). The product can be used as is for further transformations, or it can be purified by preparative HPLC (Notes 18 and 19).

2. Notes

1. All glassware was dried in an oven (110 °C), assembled, and allowed to cool under nitrogen atmosphere. All solvents used for workup need to be degassed by N₂-bubbling since the final product as well as the

intermediate are susceptible to air oxidation.

2. [60]Fullerene was provided by Frontier Carbon Corporation.

3. The checkers purchased 1,2-dichlorobenzene from Aldrich Inc. (99%) and used it without further purification. The submitters purchased 1,2-dichlorobenzene from Kanto Kagaku (>99.0%) and used it without further purification. The water content was checked with a Karl-Fischer Moisture Titrator (MK-210, Kyoto Electronics Company) to be less than 30 ppm.

4. Although the copper bromide dimethyl sulfide complex may be purchased from commercial suppliers and may work well, it is advisable to prepare it freshly because a successful reaction crucially depends on the purity of the copper complex. Copper bromide dimethyl sulfide complex, $\text{CuBr}\cdot\text{SMe}_2$, was synthesized from commercially available CuBr (Aldrich Inc. (98%, checkers); Wako Pure Chemical Industries Ltd., (submitters)) according to the following literature procedures.^{3,4} CuBr (25 g) is washed with methanol (4 x 50 mL) to remove colored impurities, and dried under reduced pressure for 1 h. The resulting green-tinged white powder of CuBr is dissolved in dimethyl sulfide (60 mL), and insoluble impurities are removed by filtration. The filtrate is diluted with hexane (200 mL) and the precipitate is collected by filtration under suction. After washing the colorless crystals five times with hexane, the light-sensitive white crystals are dried under a stream of nitrogen for 3 h. Drying under reduced pressure causes loss of the dimethyl sulfide ligand, which adversely affects the reaction. CAUTION: All procedures need to be performed in a well-ventilated hood because of the foul odor of dimethylsulfide.

5. The dimethyl sulfide complex $\text{CuBr}\cdot\text{SMe}_2$ should not be kept under reduced pressure, as it will lose the sulfide ligand.⁵

6. Anhydrous tetrahydrofuran was purchased from EMD Chemicals Inc. (checkers) or Wako Pure Chemical Industries Ltd. (submitters) and used as received. The water content was checked with a Karl-Fischer Moisture Titrator (MK-210, Kyoto Electronics Company) to be less than 30 ppm.

7. A tetrahydrofuran solution of MeMgBr was purchased from Aldrich Inc. (3 M, checkers) or Tokyo Kasei Kogyo Co., Ltd. (1 M, submitters) and used as received. Excess Grignard reagent is necessary to ensure completion of the reaction, since the copper reagent decomposes in competition with the desired reaction. The amount of excess Grignard reagent necessary is therefore reagent-dependent, and, for instance, the corresponding phenylation reaction under similar conditions may need about 8 equiv of PhMgBr and copper salt.

8. 1,3-Dimethyl-2-imidazolidinone (>98.0%) was purchased from Aldrich Inc. (checkers) or Tokyo Kasei Kogyo Co., Ltd. (submitters) and used without purification.

9. All operations from the addition of the solution of MeMgBr to the addition of the 1,2-dichlorobenzene solution of [60]fullerene are performed in about 15 min.

10. The flask is connected to a nitrogen-inlet/outlet during the reaction so that positive pressure due to ethane formation can be released.

11. Filtration is performed by silica gel flash chromatography (45 x 200 mm size) with the use of 90 g of silica gel (Sorbent Technologies Silica gel, particle size 230 – 450 mesh (checkers); Kanto Kagaku silica gel 60, spherical neutral, particle size 40 – 100 mm (submitters)).

12. The flask is washed with toluene three to ten times (the total amount is approximately 100 mL). The silica gel is repeatedly washed with toluene until the color of the filtrate turns to pale yellow.

13. The product gradually reacts with oxygen in air to afford $C_{60}Me_5O_nH$ ($n = 2-3$) in solution, therefore filtration needs to be performed as quickly as possible.

14. Care must be taken to stop evaporation when solid material just appears on the wall.

15. To minimize air oxidization of the product, methanol must be added immediately after the evaporation is complete.

16. If a part of the fine powder of the precipitate passes through the filter paper, the mother liquor can be filtered using the same filter paper.

17. HPLC analysis (flow rate: 1 mL/min) was performed on a Buckyprep column (Nacalai Tesque. Co. Ltd., 4.6 x 250 mm) with toluene/isopropanol (7/3) as eluent or an ODS column (4.6 x 250 mm) with toluene/isopropyl alcohol (3/7) as eluent.

18. The product shows the following spectroscopic properties: IR (neat) cm^{-1} : 2973, 2912, 2858, 1572, 1546, 1518, 1459, 1370, 1324, 1286, 1265, 1234, 1169, 1145, 1128, 792, 747, 684; 1H NMR (500 MHz, CS_2/CD_3COCD_3 (5%)) δ : 2.34 (s, 6 H), 2.35 (s, 6 H), 2.46 (s, 3 H), 4.50 (s, 1 H, $C_{60}-H$); ^{13}C NMR (100 MHz, CS_2/CD_3COCD_3 (5%)) δ : 27.23 (2C), 27.61 (2C), 33.14 (1C), 51.37 (1C), 51.45 (2C), 53.51 (2C), 59.75 (1C), 143.61 (2C), 144.12 (2C), 144.48 (2C), 144.53 (2C), 144.77 (2C), 144.89 (4C), 145.20 (2C), 145.42 (2C), 145.87 (2C), 145.96 (2C), 146.98 (1C), 147.14 (2C), 147.24 (2C), 148.03 (2C), 148.12 (2C), 148.29 (3C), 148.54 (2C), 148.60 (2C), 148.91 (4C), 149.10 (2C), 150.12 (2C), 154.27 (2C), 154.37 (2C), 154.62 (2C), 157.76 (2C).

19. The purity of the product in solution stored in the presence of air decreased to 80% in 24 h. Although the product is rather stable as a solid, its storage under air for several months may lead to a decrease of the purity.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Among numerous procedures to install organic residues into fullerenes, the procedure described here is unique for its selectivity and efficiency, as well as for the versatility of the product. The reaction can install five organic groups of considerable diversity into [60]fullerene in a single step in essentially quantitative yield.⁶ The same reaction puts three organic groups onto [70]fullerenes.⁷ This process represents one of the two reactions that are known for fullerenes to take place in nearly quantitative yield.⁸ The examples are shown in Table 1. For the addition of arylmagnesium bromide/CuBr•SMe₂ reagents, the 1,3-dimethyl-2-imidazolidinone additive is not necessary. However, the additive is mandatory for the MeMgBr addition.

The penta-addition product has a cyclopentadienyl moiety surrounded by the five organic groups, and it can be derivatized to a number of interesting compounds. As in standard cyclopentadiene chemistry, the cyclopentadienyl moiety can be converted to metal complexes.⁹ One striking application is the synthesis of a hybrid of ferrocene and the fullerene (bucky ferrocene).^{8b,c} The penta-organo groups can serve to protect from oxidation low-valent metal atoms attached to the center cyclopentadienide group through steric and electronic protective effects.⁸ⁱ Crystal structures of some representative metal complexes are shown below.

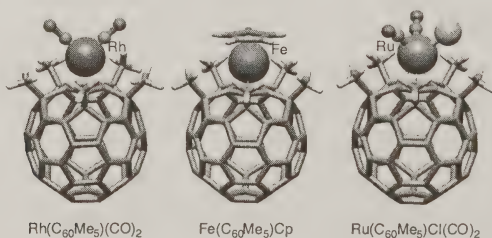
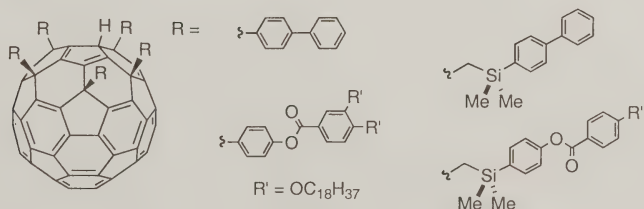


Table 1. Addition of Organocopper Reagent to Fullerenes

Fullerene	R	Product	RMgBr (equiv.)	CuBr·SMe ₂ (equiv.)	Yield (%)	reference
C ₆₀	Me ^a	C ₆₀ R ₅ H	12	12	93	this work
C ₆₀	Me ^a	C ₆₀ R ₅ H	30	30	92	6c
C ₆₀	Ph	C ₆₀ R ₅ H	15	15	99.5	6b
C ₆₀	4-CF ₃ C ₆ H ₄	C ₆₀ R ₅ H	12	12	99	6b
C ₆₀	4-MeOC ₆ H ₄	C ₆₀ R ₅ H	16	16	99	6b
C ₆₀	4-ClC ₆ H ₄	C ₆₀ R ₅ H	15	15	99.6	6b
C ₆₀	4-PhC ₆ H ₄	C ₆₀ R ₅ H	15	15	99.8	6b
C ₆₀	(<i>E</i>)-1-propenyl ^b	C ₆₀ R ₅ H	25	50	85	6d
C ₆₀	(<i>Z</i>)-1-propenyl ^b	C ₆₀ R ₅ H	25	50	77	6d
C ₆₀	(<i>E</i>)-2-phenylethenyl ^b	C ₆₀ R ₅ H	25	50	83	6d
C ₇₀	Me ^a	C ₇₀ R ₃ H	30	30	90	7b
C ₇₀	Ph	C ₇₀ R ₃ H	30	30	95	7b
C ₇₀	4-PhC ₆ H ₄	C ₇₀ R ₃ H	30	30	99	7b
C ₇₀	4-CF ₃ C ₆ H ₄	C ₇₀ R ₃ H	16	16	94	7b
C ₇₀	4-ClC ₆ H ₄	C ₇₀ R ₃ H	16	16	94	7b
C ₇₀	1-naphthyl	C ₇₀ R ₃ H	16	16	95	7b

^a1,3-Dimethyl-2-imidazolidinone was used as an additive. ^bSubstituted ethenyllithium reagents were used instead of Grignard reagents.

The fullerene compounds serve as useful building blocks in supramolecular chemistry.¹⁰ Another application of the metal complexes is the formation of bilayer vesicles upon dissolution of a potassium salt in an aqueous solution.^{9a} Upon installation of five suitable side chains, the shuttlecock-shaped penta-adduct exhibits a columnar liquid crystalline phase.^{9d,e,f}



1. Department of Chemistry, The University of Tokyo, 7-3-1 Hongo,

- Bunkyo-ku, Tokyo 113-0033, Japan.
2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA.
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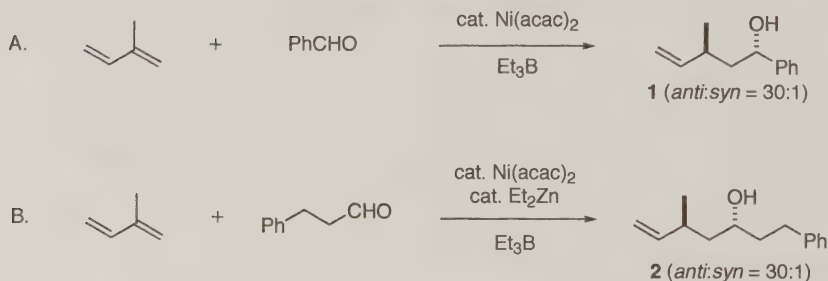
Nakamura, E. *J. Am. Chem. Soc.* **2004**, 126, 432.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

[60]Fullerene: [5,6]Fullerene-C₆₀-Ih; (99685-96-8)

NICKEL-CATALYZED HOMOALLYLATION OF ALDEHYDES WITH 1,3-DIENES

(*anti*-3-Methyl-1-phenyl-4-penten-1-ol and
anti-5-Methyl-1-phenyl-6-hepten-3-ol)



Submitted by Yoshinao Tamaru^{1a} and Masanari Kimura.^{1b}

Checked by Masakatsu Shibasaki and Noriyuki Yamagiwa.

1. Procedure

A. *3-Methyl-1-phenyl-4-penten-1-ol (1)*.² An oven-dried, 300-mL, two-necked round-bottomed flask, equipped with a rubber septum, an air condenser (fitted with a three-way stopcock connected to a nitrogen balloon), and a Teflon-coated magnetic stir bar is charged with Ni(acac)₂ (180 mg, 0.7 mmol) (Note 1). The apparatus is purged with nitrogen and the flask is charged successively via syringe with freshly distilled THF (100 mL), isoprene (5 mL, 50 mmol), and benzaldehyde (2.65 g, 25 mmol) (Note 2). Triethylborane (50 mL, 1 M hexane solution; 50 mmol) (Note 3) is added via syringe over 5 min while the solution is stirred with a magnetic stirrer. Stirring is continued for 30 h at ambient temperature. After the reaction is completed (Note 4), most of the solvents and the remaining reagents (isoprene and Et₃B) are removed with a rotary evaporator. The residual mixture is diluted with diethyl ether (60 mL). The organic phase is washed with 4 M KOH (2 x 50 mL) and brine (2 x 30 mL), and then dried over magnesium sulfate, filtered, and concentrated by rotary evaporation (Note 5). The residue is distilled by means of a Kugelrohr apparatus (90–100 °C/0.03

mmHg) to give 3-methyl-1-phenyl-4-penten-3-ol (**1**) (3.89–4.05 g, 88–92%) consisting of *anti*- and *syn*-isomers in a ratio of 30:1 (Note 6).

*B. 5-Methyl-1-phenyl-6-hepten-3-ol (2).*³ An oven-dried, 300-mL, two-necked round-bottomed flask equipped with a rubber septum, an air condenser (fitted with a three-way stopcock connected to a nitrogen balloon), and a Teflon-coated magnetic stir bar is charged with Ni(acac)₂ (192 mg, 0.75 mmol). The apparatus is purged with nitrogen and the flask is charged with freshly distilled THF (100 mL). Diethylzinc (0.75 mL, 1 M hexane solution; 0.75 mmol) is added into this solution at ambient temperature (Note 7). The color of the reaction mixture changes from yellow-green to brown. Isoprene (7.5 mL, 75 mmol) and dihydrocinnamaldehyde (3.4 g, 25 mmol) are added by syringe. Triethylborane (60 mL, 1 M hexane solution; 60 mmol) is then added via syringe over 5 min while stirring the solution with a magnetic stirrer (Note 3). Stirring is continued for 8 h at ambient temperature. After the reaction is complete (Note 8), most of the solvents and the remaining reagents (isoprene and Et₃B) are removed with a rotary evaporator. The residual solution is diluted with diethyl ether (60 mL). The organic phase is washed with 4 M KOH (2 x 40 mL) and brine (2 x 30 mL), and then dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue is distilled by means of Kugelrohr apparatus under reduced pressure (100–120 °C/0.03 mmHg) to give 5-methyl-1-phenyl-6-hepten-3-ol (**2**) (3.50–3.59 g, 68–70%) (Note 9) consisting of the *anti*- and *syn*-isomers in a ratio of 30:1 (Note 10).

2. Notes

1. Ni(acac)₂ is used as received from Aldrich Chemical Company, Inc.
2. THF (tetrahydrofuran) is distilled from sodium/benzophenone ketyl under N₂ prior to use. Benzaldehyde was used as received from Wako Pure Chemical Industry, Ltd.
3. Et₃B (1 M hexane solution) is used as received from Aldrich Chemical Company, Inc. Hydrocinnamaldehyde was used as received from Wako Pure Chemical Industry, Ltd.
4. The reaction is monitored by TLC (Merck, Silica gel 60F254). R_f (**1**) = 0.67; R_f (benzaldehyde) = 0.72: hexane/ethyl acetate = 2/1, v/v.:

visualized by a 254-nm UV lamp as well as by iodine.

5. It is crucial to wash the organic phase with a strong base, such as 4 M KOH prior to distillation. The concentrated residue obtained by washing with sat. NaHCO_3 did not withstand distillation (100 °C/0.05 mmHg) and decomposed to give an intractable mixture of products.

6. ***anti*-3-Methyl-1-phenyl-4-penten-1-ol (*anti*-1):** IR (neat) 3357 (s), 2960 (s), 2926 (s), 1494 (s), 1454 (s), 997 (s), 911 (s), 756 (s), 700 (s) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 1.01 (d, $J = 6.7$ Hz, 3 H), 1.63 (ddd, $J = 13.7$, 6.1, 6.1 Hz, 1 H), 1.83 (ddd, $J = 13.7$, 7.9, 7.9 Hz, 1 H), 1.89 (brs, 1 H), 2.20 (ddt, $J = 6.1$, 7.9, 6.7 Hz, 1 H), 4.71 (dd, $J = 6.1$, 7.9 Hz, 1 H), 4.96 (brd, $J = 10.5$ Hz, 1 H), 5.00 (brd, $J = 17.7$ Hz, 1 H), 5.77 (ddd, $J = 7.9$, 10.5, 17.7 Hz, 1 H), 7.25 - 7.34 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 20.4, 35.2, 45.9, 73.0, 113.2, 126.0, 127.6, 128.5, 144.5, 144.6. Anal. calcd. for $\text{C}_{12}\text{H}_{16}\text{O}$: C, 81.77; H, 9.15. Found: C, 81.21; H, 9.21. ***syn*-3-Methyl-1-phenyl-4-penten-1-ol (*syn*-1)** was prepared from the *anti*-isomer by Mitsunobu reactions for reference (see discussion): IR (neat) 3356 (s), 1640 (w), 1043 (s), 912 (s), 700 (s) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 1.05 (d, $J = 6.8$ Hz, 3 H), 1.61 (ddd, $J = 3.6$, 9.3, 13.9 Hz, 1 H), 1.80 (ddd, $J = 4.7$, 9.3, 13.9 Hz, 1 H), 1.83 (d, $J = 3.6$ Hz, 1 H), 2.42 (dq, $J = 8.0$, 6.8 Hz, 1 H), 4.72 (dt, $J = 9.3$, 3.6 Hz, 1 H), 5.01 (br d, $J = 10.0$ Hz, 1 H), 5.06 (br d, $J = 17.1$ Hz, 1 H), 5.73 (ddd, $J = 8.0$, 10.0, 17.1 Hz, 1 H), 7.23 - 7.38 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 21.0, 34.9, 46.1, 72.4, 113.7, 125.7, 127.4, 128.4, 143.8, 145.0. Anal. calcd. for $\text{C}_{12}\text{H}_{16}\text{O}$: C, 81.77; H, 9.15. Found: C, 81.21; H, 9.21. The diastereomeric ratio (*anti*-1/*syn*-1) was determined from the ratio of resonance integrations at 5.77 ppm (*anti*) and 5.73 ppm (*syn*) in ^1H -NMR spectra,

7. Et_2Zn (1 M hexane solution) is used as received from Aldrich Chemical Company, Inc.

8. The reaction is monitored with TLC (Merck, Silica gel 60F254). $R_f(\mathbf{2}) = 0.58$; $R_f(\text{hydrocinnamaldehyde}) = 0.50$; hexane/ethyl acetate = 2/1, v/v.: visualized by a 254-nm UV lamp as well as by iodine.

9. The submitters report an isolated yield of 80% yield.

10. ***anti*-5-Methyl-1-phenyl-6-hepten-3-ol (*anti*-2):** IR (neat) 3373 (s), 2927 (s), 1639 (s), 1603 (s), 1495 (s), 1454 (s), 913 (s), 699 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.99 (d, $J = 6.9$ Hz, 3 H), 1.42 (ddd, $J = 4.0$, 6.9,

13.8 Hz, 1 H), 1.52 (ddd, $J = 5.8, 9.8, 13.8$ Hz, 1 H), 1.65 (brs, 1 H), 1.68-1.81 (m, 2 H), 2.28-2.34 (m, 1 H), 2.65 (ddd, $J = 6.3, 9.8, 13.8$ Hz, 1 H), 2.78 (ddd, $J = 5.8, 9.8, 13.8$ Hz, 1 H), 3.68-3.73 (m, 1 H), 4.92 (dd, $J = 1.7, 10.3$ Hz, 1 H), 5.00 (brd, $J = 1.7, 17.2$ Hz, 1 H), 5.76 (ddd, $J = 8.0, 10.3, 17.2$ Hz, 1 H), 7.16-7.29 (m, 5 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 20.3, 31.9, 35.6, 39.3, 44.5, 70.0, 112.9, 125.8, 128.4, 128.4, 142.2, 145.0. Anal. calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: C, 82.30; H, 9.87. Found: C, 82.03; H, 9.58.

***syn*-5-Methyl-1-phenyl-6-hepten-3-ol (*syn*-2)** was prepared from the anti-isomer by Mitsunobu reactions for reference (see discussion): IR (neat) 3354 (s), 1641 (m), 1030 (m), 997 (s), 914 (s), 698 (s) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 1.02 (d, $J = 6.4$ Hz, 3 H), 1.43 (dm, $J = 13.9$ Hz, 1 H), 1.50 (dm, $J = 13.9$ Hz, 1 H), 1.70-1.78 (m, 2 H), 2.40 (dq, $J = 8.0, 6.4$ Hz, 1 H), 2.66 (dm, $J = 13.9$ Hz, 1 H), 2.78 (dm, $J = 13.9$ Hz, 1 H), 3.68 (br s, 1 H), 4.96 (br d, $J = 10.1$ Hz, 1 H), 5.03 (d, $J = 17.2$ Hz, 1 H), 5.67 (ddd, $J = 8.0, 10.1, 17.2$ Hz, 1 H), 7.15-7.29 (m, 5 H); ^{13}C NMR (120 MHz, CDCl_3) δ : 21.1, 32.1, 34.8, 39.6, 44.3, 69.3, 113.3, 125.6, 128.2, 142.0, 143.9; Anal. calcd. for $\text{C}_{14}\text{H}_{20}\text{O}$: C, 82.30; H, 9.87. Found: C, 82.03; H, 9.58. The diastereomeric ratio (*anti*-2/*syn*-2) was determined from the ratio of resonance integrations at 5.76 ppm (*anti*) and 5.67 ppm (*syn*) in ^1H -NMR spectra.

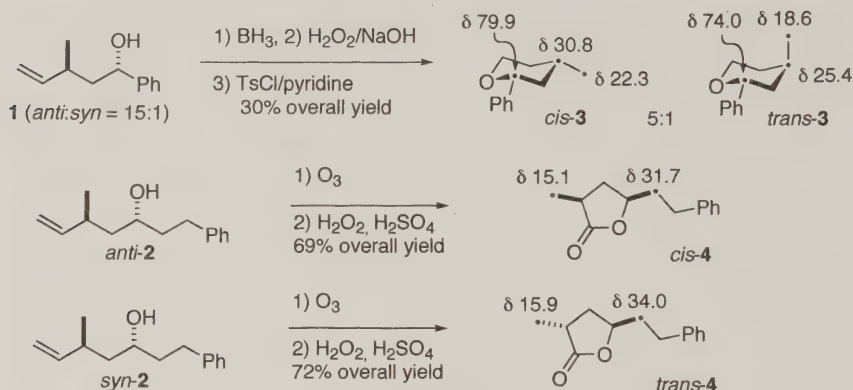
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The structures of the minor components of **1** and **2** were confirmed to be the diastereomeric isomers, *syn*-1 and *syn*-2, respectively, by comparison of the spectral data with those of authentic samples prepared by the Mitsunobu inversion (PhCO_2H , diethyl azodicarboxylate, Ph_3P) followed by hydrolysis (NaOH , $\text{EtOH-H}_2\text{O}$): *anti*-1:*syn*-1 = 1:30 in 79% overall yield from *anti*-1:*syn*-1 = 30:1; *anti*-3:*syn*-3 = 1:30 in 72% overall yield from

anti-**3**:*syn*-**3** = 30:1. The structure determination of **1** and **2**⁴ relied on the ¹³C NMR chemical shifts of their cyclic derivatives **3** and **4**, respectively (Scheme 1).



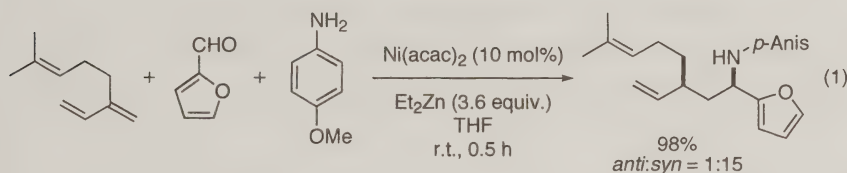
Scheme 1

Transformation of **1** and **2** into Heterocycles **3** and **4** and their ¹³C Chemical Shifts (δ in ppm, 100 MHz in CDCl₃).

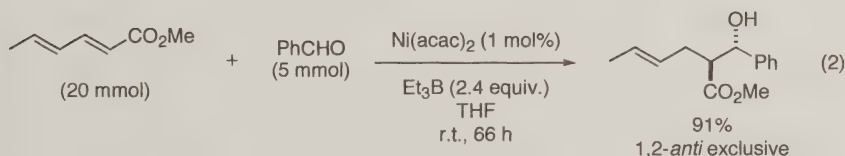
Bishomoallyl alcohols and ethers are ubiquitous structural motifs of natural products, especially of polyether antibiotics and acetogenin-derived natural products.⁵ The present nickel-catalyzed homoallylation of aldehydes with isoprene (and other 1,3-dienes)⁶ provides a powerful method for constructing such classes of compounds.⁷ The reaction shows high 1,3-diastereoselectivity furnishing 1,3-*anti*-4-penten-1-ol products with as high as 95 – 100% stereoselectivity.

Three variations on the homoallylation procedure are available and appropriate choice of the method to be applied requires consideration of the reactivity of the aldehyde. For reactive aldehydes (aromatic and unsaturated aldehydes), procedure A is the method of choice.² A second (unchecked) procedure is particularly effective for the homoallylation of relatively unreactive and sterically hindered aliphatic aldehydes, as well as ketones.³ This second procedure is sometimes plagued with a side reaction resulting from ethylation of the aldehyde. This problem is most apparent when reactive primary and secondary aliphatic aldehydes are used. For such cases, procedure B is recommended, because ethylation can be avoided almost completely. Thus, these three methods complement one another.

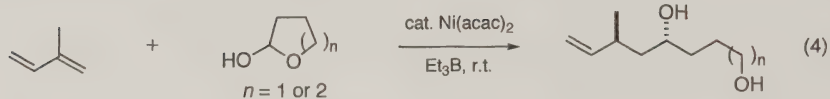
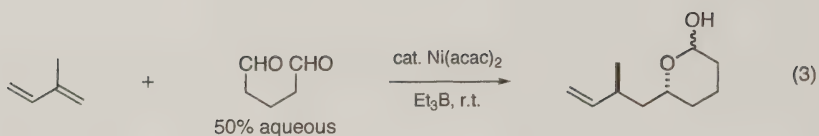
A variation on these procedures has been successfully applied to the homoallylation of aldimines formed *in situ* from aromatic aldehydes and anisidine. Good yields of 1,3-*syn*-bishomoallyl amines are furnished with excellent stereoselectivity. Aldimines are generally by far less reactive than aldehydes. Interestingly, the sense of stereoselection is opposite to that observed for aldehydes (Eq 1).⁸



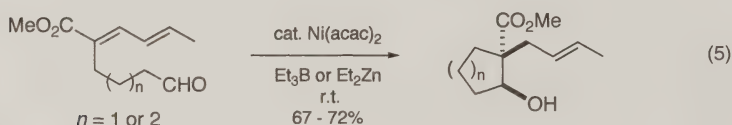
Sorbic acid methyl ester, an electron-deficient diene, engages by (Eq 2) reacting regioselectively at the C2 position with high 1,2-*anti* stereoselectivity. All results to date suggest that unsymmetrically substituted 1,3-dienes react with aldehydes regioselectively at the terminus bearing the highest electron density.



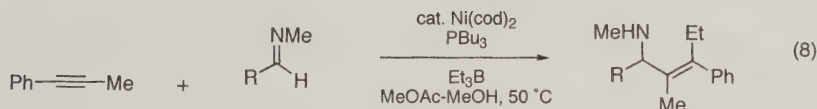
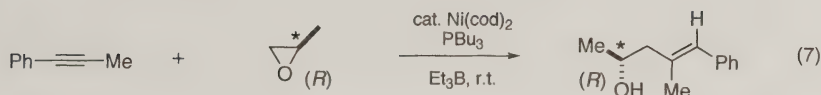
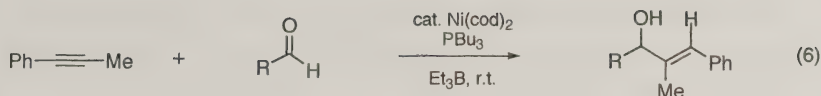
Triethyl borane (Et_3B) is compatible with water; hence, the method described in procedure A can be applied to the homoallylation of aldehydes that are stable only in water.⁹ For example, in the presence of a catalytic amount of $\text{Ni}(\text{acac})_2$ and a stoichiometric amount of Et_3B , isoprene reacts regioselectively at the C1 position with a commercial 50% aqueous solution of glutaraldehyde to provide a 1,3-*anti*-bishomoallyl alcohol. Cyclic hemiacetals ($n = 1$ or 2) undergo the homoallylation with isoprene to form bishomoallylic diols with excellent 1,3-asymmetric induction (Eq 4).



The protocol for the intermolecular homoallylation of aldehydes with 1,3-dienes can be applied successfully to an intramolecular version of ω -dienyl aldehydes forming five- and six-membered cycloalkanols (Eq 5).¹⁰



The combination of nickel and Et₃B has been proved to be applicable to the reductive coupling of alkynes and aldehydes to provide allylic alcohols with high regio- and stereoselectivities (Eq 6).¹¹ The procedure is extended to the asymmetric synthesis of allyl alcohols and is applied to the total synthesis of natural products.¹² Under similar conditions, enantioenriched epoxides undergo the reductive coupling with alkynes and provide homoallyl alcohols with complete preservation of the original chirality (Eq 7).¹³ In contrast to the reactions with aldehydes and epoxides, the reaction with aldimines delivers the ethyl group of Et₃B, instead of hydrogen, at the distal carbon of alkynes to give rise to stereochemically defined allyl amines (Eq 8).¹⁴



- (a) Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan. tamaru@net.nagasaki-u.ac.jp; (b) Graduate School of Science and Technology, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan. masanari@net.nagasaki-u.ac.jp
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Appendix

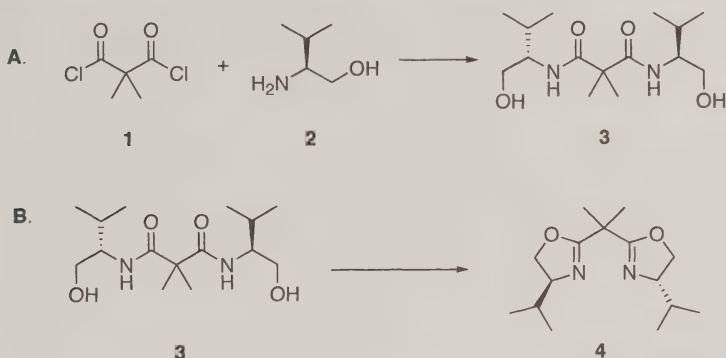
Chemical Abstracts Nomenclature (Registry Number)

Diethylzinc (1.0 M solution in hexanes): FLAMMABLE LIQUID; Zinc, diethyl; (557-20-0)

Triethylborane (1.0M solution in hexanes): FLAMMABLE LIQUID; Borane, triethyl; (97-94-9)

Nickel(II) acetylacetonate: CANCER SUSPECT AGENT: Bis(2,4-pentanedionate), nickel(II); (3264-82-2)

SYNTHESIS OF (–)-(S,S)- BIS(4-ISOPROPYLOXAZOLINE) [[4S, 4S′)-2,2′-(Propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole)]



Submitted by David A. Evans,¹ Keith A. Woerpel,^{1,2} Bernd Nosse,³ Andreas Schall,³ Yogesh Shinde,³ Eva Jezek,³ Mohammad Mahbubul Haque,³ R. B. Chhor,³ and Oliver Reiser.³
Checked by Peter Wipf and Nilukshi Jayasuriya.⁴

1. Procedure

A. (–)-(S,S)-N,N′-Bis(1-hydroxymethyl-2-methylpropyl)-2,2-dimethylmalonamide (**3**): An oven-dried 250 mL, 3-necked round-bottom flask equipped with a stirring bar and two 50 mL pressure-equalizing addition funnels connected to a mineral oil bubbler is purged with nitrogen and charged with (L)-valinol (**2**, 5.13 g, 0.050 mol, Note 1). The flask is immersed in an ice bath at 0 °C and triethylamine (17.4 mL, 0.124 mol, Note 2) is added dropwise via the first addition funnel. 2,2-Dimethylpropanedioyl dichloride (3.3 mL, 0.25 mol, Note 3) in dry dichloromethane (25 mL, Note 4) is then added dropwise over 25 minutes via the second addition funnel. The internal temperature increases from 0 °C to 10 °C during the addition. Subsequently, the ice bath is removed and the reaction mixture is allowed to warm to room temperature. Stirring is continued for 45 min, resulting in a colorless precipitate that is dissolved by addition of dry dichloromethane (120 mL). After addition of aqueous HCl (1 N, 30 mL), the aqueous layer is separated and extracted with dichloromethane (3 x 15 mL). The combined organic layers are washed with saturated NaHCO₃ solution (30 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to afford crude **3** as a pale yellow solid. Recrystallization of the crude product

from ethyl acetate (40 mL) yields **3** (4.30 g, 14.2 mmol, 57%) as white crystals. The mother liquor is concentrated and the residue recrystallized from ethyl acetate (10 mL) to yield a second crop of **3** (1.60 g, 5.27 mmol, 21%); the process is repeated to yield a third crop of **3** (0.440 g, 1.45 mmol, 6%, total yield: 6.40 g, 21.1 mmol, 84%, Note 5).

B. (-)-(S,S)-Bis(4-isopropylloxazoline) (4): An oven-dried 500 mL, 2-necked round-bottom flask equipped with a stirring bar and a 50 mL, pressure-equalizing addition funnel connected to a mineral oil bubbler is purged with nitrogen and charged with (-)-(S,S)-N,N'-bis-(1-hydroxymethyl-2-methylpropyl)-2,2-dimethylmalonamide (**3**, 5.5 g, 18.4 mmol), 4-dimethylaminopyridine (0.204 g, 1.67 mmol, Note 6) and dry dichloromethane (130 mL, Note 4). The flask is immersed in a water bath at room temperature and triethylamine (10.25 mL, 73.4 mmol, Note 2) is added slowly via syringe. Subsequently, tosyl chloride (7.10 g, 37 mmol, 2.0 equiv., Note 7), dissolved in dry dichloromethane (15 mL), is added dropwise over 30 minutes via the addition funnel. After completion of the addition, the funnel is rinsed with dry dichloromethane (2.5 mL) and the reaction mixture is stirred for an additional 27 h at room temperature (Note 8). The reaction mixture is treated with saturated NH₄Cl solution (70 mL) followed by water (40 mL). The aqueous layer is separated and extracted with dichloromethane (3 x 55 mL), and the combined organic layers are dried over MgSO₄. The organic solution is filtered and concentrated under vacuum. The oily residue is treated with hot pentane (40 mL, Note 9), stirred for 5 min and the supernatant liquid is decanted. This procedure is repeated three times and the collected pentane layers are combined and concentrated under vacuum to yield **4** (4.05 g, 15.2 mmol, 83%, Note 10) as a colorless oil.

2. Notes

1. (L)-Valinol was prepared from (L)-valine in 81% yield in an analogous way to the reduction of (*S*)-*tert*-leucine to (*S*)-*tert*-leucinol according to Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541, or purchased from Aldrich Chemical Company, Inc.

2. Triethylamine was obtained from Alfa Aesar and was distilled prior to use from calcium hydride under nitrogen.

3. 2,2-Dimethylpropanedioyl dichloride was purchased from Aldrich Chemical Company, Inc. or synthesized from 2,2-dimethylmalonic acid in 90% yield according to Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.

4. Dichloromethane was purified by filtration through activated alumina.

5. Physical properties and spectral data for **3** are as follows: R_f 0.25 (EtOAc:MeOH, 95:5); $[\alpha]_D^{24}$ -6.0 (c 0.50, CH₂Cl₂); mp 98–99 °C; ¹H NMR (300 MHz, CDCl₃) δ : 0.92 (d, J = 6.8 Hz, 6 H), 0.96 (d, J = 6.8 Hz, 6 H), 1.50 (s, 6 H), 1.82 (oct, J = 6.8 Hz, 2 H), 2.66 (bs, 2 H), 3.52 (m, 2 H), 3.69–3.86 (m, 4 H), 6.41 (d, J = 8.6 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ : 18.8, 19.6, 23.7, 29.1, 50.2, 57.1, 63.5, 174.5; IR (KBr) cm⁻¹ 3349, 3380, 2962, 2886, 1658, 1530, 1049, 1033; MS (ES) m/z (%) 405.2 (20), 325.2 ([M+Na]⁺, 100), 285.2 (10); HRMS (ES) calcd. for C₁₅H₃₀N₂O₄Na 325.2103, found 325.2084; Anal. calcd. for C₁₅H₃₀N₂O₄: C, 59.57; H, 10.00; N, 9.26. found: C, 59.01; H, 10.12; N, 9.11.

6. 4-Dimethylaminopyridine was obtained from the Aldrich Chemical Company, Inc and used as received.

7. Tosyl chloride was obtained from the Aldrich Chemical Company, Inc and used as received.

8. After the reaction mixture was stirred for 27 h, the submitters noticed crystalline solid precipitate. The solid precipitate was dissolved by adding dichloromethane (50 mL) prior to workup. The checkers, however, did not observe any precipitate.

9. In some experiments, a cloudy precipitate was formed, which was then dissolved in dichloromethane (2.5 mL per mmol of **3**) prior to workup.

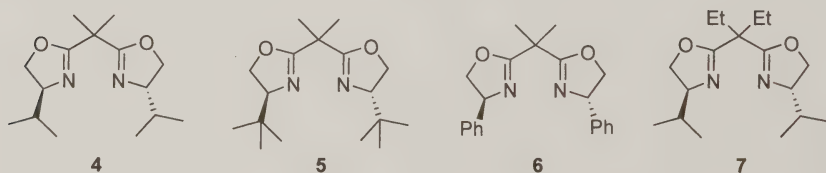
10. An analytically pure sample for characterization purposes was obtained by Kugelrohr distillation (95–100 °C, 0.5 mmHg) of the crude material. Physical properties and spectral data for **4** are as follows R_f 0.25 (CH₂Cl₂/MeOH, 19:1); $[\alpha]_D^{24}$ -107.5 (c 1.0, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ : 0.85 (d, J = 6.8 Hz, 6 H), 0.91 (d, J = 6.8 Hz, 6 H), 1.51 (s, 6 H), 1.88–1.73 (m, 2 H), 4.06–3.93 (m, 4 H), 4.26–4.15 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ : 17.3, 18.5, 24.4, 32.2, 38.5, 69.9, 71.5, 168.7; IR (film) cm⁻¹ 3308, 2960, 2874, 1746, 1525, 1353, 1303, 1037, 1017, 895, 815, 714; MS (EI) m/z (%) 266 (M⁺, 15), 265 (30), 223 (100), 195 (30), 155 (65), 137 (97), 110 (50); HRMS (EI) calcd for C₁₅H₂₆N₂O₂ 266.1994, found 266.1987; Anal. calcd for C₁₅H₂₆N₂O₂: C, 67.63; H, 9.84; N, 10.52. found C, 66.65; H, 9.81; N, 10.08.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Since the discovery of oxazolines as ligands for catalysis,⁵ bis(oxazolines)⁶ have proved to be privileged structures because they promote a great number of metal-catalyzed transformations with unprecedented selectivity. Most commonly, bis(oxazolines) can be obtained from amino alcohols, either by a two-step condensation/cyclization sequence with acid chlorides as described here, or by condensation with dinitriles in the presence of a metal salt such as zinc(II) chloride⁷, trifluoromethanesulfonic acid⁸ or stepwise formation of the corresponding imidates⁹ followed by cyclization. While the commercially available *tert*-butyl-substituted bis(oxazoline) **5**^{10,11} often gives rise to the highest selectivities, a number of applications¹² have been developed in which the bis(4-isopropylloxazoline) **4** or the phenyl-substituted bis(oxazoline) **6** will give similar or even better results. Moreover, for the synthesis of **5** the unnatural and therefore expensive amino acid *tert*-leucine is required. Consequently, bis(4-isopropylloxazoline) **4**, available as either enantiomer from inexpensive (*S*)- or (*R*)-valine, is an attractive alternative for large scale applications if equally good enantioselectivity can be achieved.



The procedure described here for bis(4-isopropylloxazoline) **4** closely resembles the previously reported protocols for the bis(4-ethylloxazoline) **7**¹³ and the bis(4-*tert*-butylloxazoline) ligand **5**.¹⁰ The main differences can be found in the workup conditions, which accommodate the quite different solubility and crystallization properties of intermediates and final ligands.

1. Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, MA 02139, USA
2. New address: Department of Chemistry, University of California, Irvine, CA 92697, USA
3. Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany.
4. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA.
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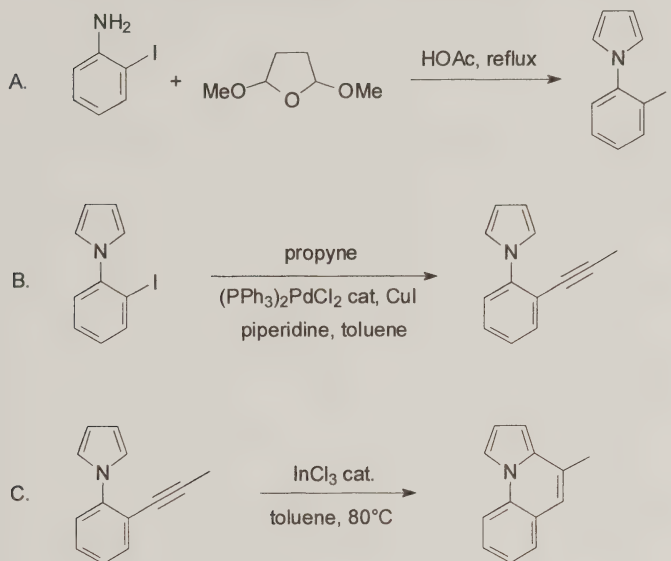
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

2,2-Dimethyl-propanedioyl dichloride : Propanedioyl dichloride, dimethyl-;
5659-93-8

(L)-Valinol: 1-Butanol, 2-amino-3-methyl-, (2*S*)-; 2026-48-4

INDIUM-CATALYZED CYCLOISOMERIZATION: PREPARATION OF 4-METHYLPYRROLO[1,2-*a*]QUINOLINE



Submitted by Alois Fürstner, Victor Mamane, Günter Seidel, and Daniel Laurich.

Checked by Scott E. Denmark and Jack Hung-Chang Liu.

1. Procedure

A. *1-(2-Iodophenyl)pyrrole*. A 50-mL, three-necked, round-bottomed, flame-dried flask equipped with a Teflon-coated stirbar, a glass stopper, an addition funnel and a reflux condenser is charged with 2-iodoaniline (12.5 g, 57.1 mmol) (Notes 1, 2) and glacial acetic acid (12.5 mL, Note 1). The resulting solution is heated to reflux before 2,5-dimethoxytetrahydrofuran (7.8 mL, 59.0 mmol, Note 1) is added over a period of 10 min via the dropping funnel and reflux is continued for 5 min once the addition is complete. The addition funnel and reflux condenser are replaced by an inlet for a thermocouple and a distillation head with condenser, respectively, and the acetic acid is slowly removed by distillation under reduced pressure (15 mmHg, bath temperature about 50 °C) over a period of approximately 4 h. During this time, the internal temperature slowly reaches 50 °C. The remaining brown residue is transferred to a 25-mL round-bottomed flask and

is purified by short-path distillation in vacuum (0.04 mmHg, Note 3). The fraction distilling at 90–102 °C is collected to give 1-(2-iodophenyl)pyrrole as a brown liquid (9.78–10.12 g, 64–66%) (Notes 4, 5).

B. *1-(2-(1-Propynyl)phenyl)pyrrole*. A flame-dried 250-mL, two-necked, round-bottomed flask equipped with a magnetic stirbar, a gas dispersion tube (5 mm OD, Note 6), and a bubbler-sealed gas outlet is charged sequentially with 1-(2-iodophenyl)pyrrole (8.98 g, 33.4 mmol), piperidine (10 mL, Note 1), $(\text{PPh}_3)_2\text{PdCl}_2$ (1.20 g, 1.67 mmol, Note 1), CuI (318 mg, 1.67 mmol, Note 1) and toluene (90 mL, Note 1) to give a homogeneous reddish solution. Propyne is bubbled through this solution for 90 min at 0.1 L/min via the dispersion tube until the reaction mixture turns black (Notes 7, 8). For workup, the flask is vented, the reaction mixture is filtered through a short pad of silica (approximately 30 g) which is carefully rinsed with *tert*-butyl methyl ether (350 mL). The combined filtrates are transferred into a 1-L separatory funnel and are successively washed with water (2 x 200-mL portions) and brine (350 mL) before being dried over Na_2SO_4 and evaporated. The remaining orange liquid is transferred to a 25-mL round-bottomed flask and is purified by short-path distillation in vacuum (Note 3) to give 1-(2-(1-propynyl)phenyl)pyrrole as a pale yellow liquid (bp 70–75 °C, 0.005 mm Hg) (4.56–4.72 g, 75–78%, Notes 5, 9).

C. *4-Methylpyrrolo[1,2-a]quinoline*. A 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet, a glass stopper, a stopcock gas inlet and a Teflon-coated magnetic stirbar is evacuated and flame-dried before it is flushed with argon and allowed to cool to ambient temperature. The flask is charged with 1-(2-(1-propynyl)phenyl)pyrrole (4.53 g, 25 mmol), toluene (100 mL, Note 1) and InCl_3 (277 mg, 1.25 mmol, Note 10) and the resulting mixture is stirred at 80 °C bath temperature for 4 h until GC analysis shows complete conversion of the substrate (Note 11). For workup, the dark mixture is filtered through a pad of silica gel (5 cm x 3 cm, approximately 30 g), which is then carefully rinsed with toluene (150 mL). The crude product was obtained as a yellow solid after removal of the solvent under reduced pressure. The product is dissolved in toluene (20 mL) and this solution is adsorbed on silica gel (approximately 10 g) and the resulting slurry is evaporated to dryness. The adsorbate is placed in a Soxhlet thimble (8.0 cm x 3.5 cm) and is extracted with pentane (80 mL, Note 1) for 18 h using a Soxhlet apparatus of ca. 50 mL inner volume (Note 12). Evaporation of the resulting pentane extract provides 4-methylpyrrolo[1,2-a]quinoline as a pale yellow solid, which is pure enough for most applications (mp 63–65°C, $\geq 95\%$ by GC, Note 11)

(4.12 g, 91%). Analytically pure material is obtained by subsequent sublimation (60 °C bath temperature, 5×10^{-3} mmHg for 3.5 h, Note 13) as a white solid (3.05 g, 67%, Notes 14-16), mp 67–68 °C.

2. Notes

1. 2-Iodoaniline (>98%) was purchased from Aldrich Chemical Co. or from Lancaster. 2-Iodoaniline was recrystallized by dissolving the commercial material in benzene with stirring in a round-bottomed flask, in a 50 °C oil bath. For each gram of 2-iodoaniline, 1 mL of benzene was used. To the dark brown solution of 2-iodoaniline was then slowly added petroleum ether with stirring. Approximately four times the volume of benzene was added. This mixture was allowed to cool to room temperature and was then cooled in –20 °C for approximately 4 hours. The dark brown crystals were filtered off through a coarse fritted funnel, and were further purified by sublimation under high vacuum for approximately 2 to 2.5 h (oil bath temperature: 50–55 °C, cold finger of the sublimator cooled by a dry ice-acetone bath). The melting point of the purified material was 56–57 °C and was significantly less colored. Copper(I) iodide (CuI, 99.999%), $(\text{PPh}_3)_2\text{PdCl}_2$ (99.99%) (Aldrich Chemical Co.), glacial acetic acid (99%, Fluka), 2,5-dimethoxytetrahydrofuran (99%, *cis/trans* mixture, Acros Organics), and piperidine (99%, Aldrich Chemical Co.) were purchased from the suppliers indicated. 2,5-Dimethoxytetrahydrofuran was purified by short path distillation. Other chemicals were used as received. Toluene and pentane were dried by distillation over Na/benzophenone prior to use.

2. For Step A, the checkers were not able to reproduce the yield when the reaction was carried out on 114.0 mmol scale; considerably more unreacted 2-iodoaniline remained than when the reaction was carried out on 57.0 mmol scale. This was most likely due to the less efficient heat transfer into a 100-mL flask. Consequently, the distillate was a mixture of starting material and product.

3. The short path distillation was performed with a one-piece distillation apparatus consisting of a vacuum-jacketed distillation head and short (approximately 3 cm) condenser arm. This equipment enables adiabatic distillation and is commercially available from Ace Glass (catalog no. 9317-42).

4. ^1H NMR (500 MHz, CDCl_3) δ : 6.35 (t, $J = 2.1$ Hz, 2 H), 6.82 (t, $J = 2.1$ Hz, 2 H), 7.11 (ddd, $J = 9.0, 7.9, 1.7$ Hz, 1 H), 7.31 (dd, $J = 7.8, 1.6$ Hz, 1 H), 7.42 (ddd, $J = 8.8, 7.7, 1.4$ Hz, 1 H), 7.95 (dd, $J = 8.0, 1.4$ Hz, 1 H);

^{13}C NMR (126 MHz, CDCl_3) δ : 96.0, 109.3, 122.3, 128.2, 129.1, 129.6, 140.1, 144.2; MS (EI) m/z (relative intensity): 269 (100%, $[\text{M}^+]$), 142 (35%), 115 (62%); HRMS (EI) m/z , calcd for $\text{C}_{10}\text{H}_8\text{NI}$: 268.9702; found: 268.9701; IR (film): 3101, 1582, 1494, 1438, 1072, 1012, 924, 760, 724 cm^{-1} . Anal. calcd for $\text{C}_{10}\text{H}_8\text{IN}$ (269.08): C, 44.64; H, 3.00; N, 5.21. Found: C, 44.65; H, 2.77; N, 5.02.

5. The product is stable for extended periods of time when kept in a refrigerator.

6. The gas dispersion tube was purchased from ACE Glass (catalog no. 9435-78).

7. Propyne purchased from Matheson Inc. was used without further purification.

8. A flow-meter (Matheson Tri-Gas: PM-1000, part no. MN11E101N201) showed that a total of approximately 9 L of propyne was passed through the solution. If a less vigorous stream of propyne is chosen, then the reaction time will increase accordingly. In all cases, however, the formation of a black precipitate indicated complete conversion.

9. ^1H NMR (500 MHz, CDCl_3) δ : 2.03 (s, 3 H), 6.36 (dt, $J = 2.5$, 1.3 Hz, 2 H), 7.16 (dt, $J = 2.2$, 1.1 Hz, 2 H), 7.25 (dt, $J = 7.5$, 1.4 Hz, 1 H), 7.31 (dd, $J = 8.0$, 1.0 Hz, 1 H), 7.36 (dt, $J = 8.1$, 1.5 Hz, 1 H), 7.55 (d, $J = 7.8$ Hz, 1 H); ^{13}C NMR (126 MHz, CDCl_3) δ : 4.7, 76.8, 91.0, 109.2, 118.8, 121.8, 125.0, 126.3, 128.7, 134.2, 142.0; MS (EI) m/z (relative intensity): 181 (100%, $[\text{M}^+]$), 180 (95%), 166 (3%), 154 (18%), 152 (11%), 140 (2%), 127 (4%), 115 (3%), 89 (5%), 77 (7%); HRMS (EI) m/z , calcd for $\text{C}_{13}\text{H}_{11}\text{N}$: 181.0891, found: 181.0886; IR (film): 3102, 2914, 2849, 2226, 1599, 1501, 1478, 1332, 1102, 1070, 761, 725 cm^{-1} . Anal. calcd for $\text{C}_{13}\text{H}_{11}\text{N}$ (181.24): C, 86.15; H, 6.12; N, 7.73; Found: C, 86.02; H, 6.12; N, 8.04.

10. InCl_3 (99.999%, Strem Chemicals) was used as received. Due to its hygroscopic character, this compound was kept in a dry box.

11. Occasionally, the reaction time was found to be somewhat longer. The progress of the reaction and the purity of the product can be monitored by GC (Hewlett-Packard HP-5, 5% phenylmethylsiloxane column: 50 m, 0.25 mm), temperature program: 70 $^\circ\text{C} \rightarrow 270$ $^\circ\text{C}$, 20 $^\circ\text{C}/\text{min}$, then 270 $^\circ\text{C}$ for 6.0 min; retention time: 11.81 min (starting material), 14.24 min (product).

12. In a second run, the checkers found that a higher yield (4.20 g, 93%) could be obtained by exhaustive Soxhlet extraction for 48 h. Sublimation of this material (oil bath: 50–60 $^\circ\text{C}$, 7 h), afforded 3.97 g (88%) of the product as a white solid.

13. The sublimation was performed by immersing a large side-armed test tube (42 mm x 175 mm) containing the crude product in an oil bath and subliming the product under reduced pressure onto the cold wall of a smaller test tube (25 mm x 150 mm) cooled with a dry-ice/acetone slush. The smaller test tube, which served as a cold finger, was secured by a large rubber stopper. During the sublimation, the bath temperature should not exceed 60 °C to avoid undue decomposition. The purity of the material can be checked by GC (Note 11).

14. The submitters found that analytically pure material (2.49 g, 55%) could also be obtained by recrystallization from hexanes (15 mL).

15. In solid form, the product can be stored in a refrigerator for extended periods of time. However, the product is sensitive in solution to traces of acid present in CDCl_3 that has not been rigorously purified.

16. ^1H NMR (500 MHz, CDCl_3) δ : 2.45 (d, $J = 1.3$ Hz, 3 H), 6.54 (dd, $J = 3.8, 1.4$ Hz, 1 H), 6.81 (dd, $J = 3.8, 3.7$ Hz, 1 H), 6.83 (s, 1H), 7.30 (dt, $J = 7.5, 1.1$ Hz, 1 H), 7.46 (dt, $J = 7.8, 1.5$ Hz, 1 H), 7.60 (dd, $J = 7.8, 1.4, 1$ H), 7.87 (d, $J = 1.3$ Hz, 1 H), 7.87 (d, $J = 7.7$ Hz, 1 H); ^{13}C NMR (126 MHz, CDCl_3) δ : 18.5, 101.3, 112.5, 112.6, 114.2, 117.7, 123.7, 124.6, 127.0, 128.0, 128.1, 129.4, 132.7; MS (EI) m/z (relative intensity): 181 (100%, $[\text{M}^+]$), 180 (42%), 152 (8%), 91 (7%), 77 (7%); HRMS (EI) m/z , calcd for $\text{C}_{13}\text{H}_{11}\text{N}$: 181.0891; found: 181.0890; IR (film): 3142, 1608, 1541, 1486, 1458, 1419, 1366, 1192, 1088, 867, 840, 774, 753, 739, 703 cm^{-1} . Anal. calcd for $\text{C}_{13}\text{H}_{11}\text{N}$ (181.24): C, 86.15; H, 6.12; N, 7.73. Found: C, 86.03; H, 6.15; N, 7.85.

Safety and Waste Disposal Information

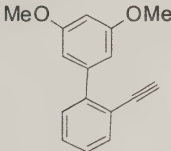
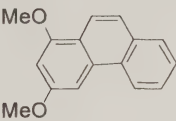
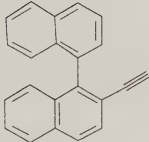

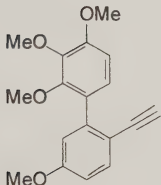
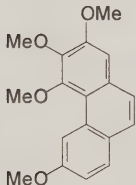
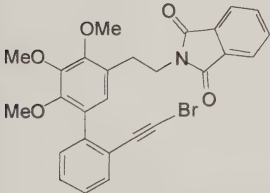
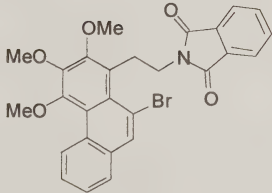
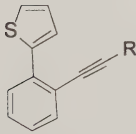
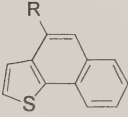
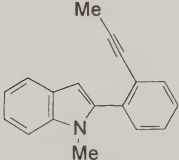
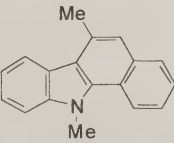
All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

The ability of “soft” metal salts such as PtCl_2 , AuCl_3 or InCl_3 to render alkynes susceptible to attack by (tethered) nucleophiles such as alkenes, allyl ethers, or aromatic systems has been recognized only recently.²⁻⁴ The ensuing skeletal rearrangements are inherently attractive for increasing molecular complexity. In this context, it has been shown that readily available biaryl derivatives containing an alkyne unit at one of their

ortho-positions are converted into substituted phenanthrenes, or heterocyclic congeners thereof, on exposure to catalytic amounts of these salts in an inert solvent.⁵⁻⁷ The most widely applied catalyst for this purpose is PtCl₂, although GaCl₃ and InCl₃ tend to give higher yields with heteroaromatic substrates as well as with biaryl derivatives bearing halo-alkynes. Such metal-catalyzed transformations accommodate substantial structural variations as can be seen from the selected examples compiled in the Table. In addition to a host of phenanthrene derivatives, substituted helicenes, benzoindoles, benzocarbazoles, naphthothiophenes, or pyrrolo[1,2-*a*]quinolines can be obtained in good to excellent yields.⁵⁻⁷ Since the latter class of heterocycles is endowed with promising biological activities but is difficult to make by more conventional methodology,⁸ the procedure detailed above provides a good illustration for the advantages associated with this novel catalytic approach.

TABLE. Selected Examples of Phenanthrenes and Polycyclic Heteroarenes Formed by Metal-Catalyzed Cycloisomerization Reactions⁵⁻⁷

Substrate	Catalyst	Product	Yield
	PtCl ₂		73%
	PtCl ₂		56%
	PtCl ₂		86%
	PtCl ₂		87%
	PtCl ₂ InCl ₃		54% (R = H) 83% (R = Ph)
	PtCl ₂		93%

1. Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim, Germany.
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

2-Iodoaniline: Benzenamine, 2-iodo-; (615-43-0)

2,5-Dimethoxytetrahydrofuran: Furan, tetrahydro-2,5-dimethoxy-;
(696-59-3)

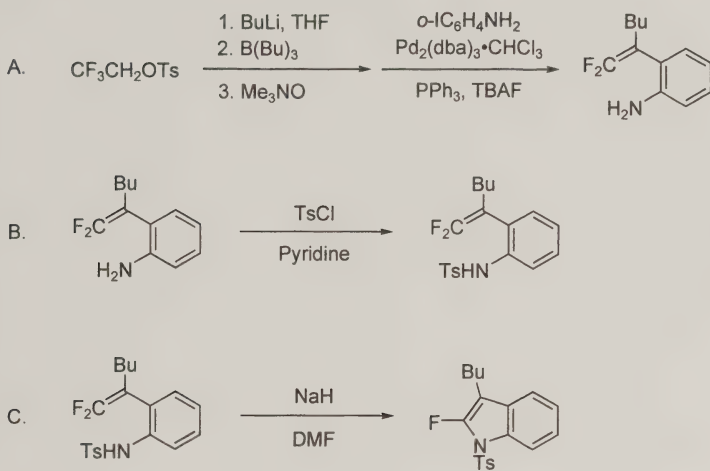
1-(2-Iodophenyl)pyrrole: 1H-Pyrrole, 1-(2-iodophenyl)-; (157017-41-9)
(PPh₃)₂PdCl₂: Palladium, dichlorobis(triphenylphosphine)-; (13965-03-2)

1-(2-(1-propynyl)phenyl)pyrrole: 1H-Pyrrole, 1-[2-(1-propynyl)phenyl]-;
(796843-21-5)

4-Methylpyrrolo[1,2-a]quinoline; (796843-24-8)

InCl₃: Indium chloride; (10025-82-8)

**5-endo-trig CYCLIZATION OF 1,1-DIFLUORO-1-ALKENES:
SYNTHESIS OF 3-BUTYL-2-FLUORO-1-TOSYLINDOLE
(1*H*-Indole, 3-butyl-2-fluoro-1-[(4-methylphenyl)sulfonyl]-)**



Submitted by Junji Ichikawa, Ryo Nadano, Takashi Mori, and Yukinori Wada.¹

Checked by Sigrid Holle and Alois Fürstner.

1. Procedure

A. *o*-(1,1-Difluorohex-1-en-2-yl)aniline. A 1-L, three-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirbar, two pressure-equalizing dropping funnels, and a reflux condenser fitted with an argon stopcock inlet. The system is flame-dried and flushed with argon. The flask is charged with anhydrous tetrahydrofuran (200 mL) (Note 1) and 2,2,2-trifluoroethyl *p*-toluenesulfonate (15.3 g, 60 mmol) (Note 2), and the solution is cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice–acetone bath. Butyllithium (76.8 mL, 1.64 M in hexane, 126 mmol) (Note 3) is added via one of the dropping funnels over 10 min (Note 4) and the resulting mixture is stirred for an additional 20 min. Then tributylborane (66.0 mL, 1.0 M in THF, 66 mmol) (Note 5) is added via the other dropping funnel at $-78\text{ }^{\circ}\text{C}$ over 3 min. After being stirred for 1 h, the reaction mixture is warmed to room temperature and stirred for an additional 3 h to generate 2,2-difluorovinylborane. This solution of 2,2-difluorovinylborane is cooled in an ice bath prior to addition of trimethylamine oxide (10.9 g, 145 mmol) (Note 6). The reaction mixture

is stirred at 0 °C for 2 h, and then allowed to warm to room temperature. Triphenylphosphine (PPh_3 , 2.52 g, 9.60 mmol) (Note 7) and tris(dibenzylideneacetone)dipalladium-chloroform (1/1) ($\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$, 2.48 g, 2.40 mmol) (Note 8) are added in this order, and the mixture is stirred for 15 min. To the mixture are added *o*-iodoaniline (9.20 g, 42.0 mmol) (Note 9) and tetrabutylammonium fluoride (168 mL, 1.0 M in tetrahydrofuran, 168 mmol) (Note 10). After being stirred at room temperature for 15 min, the resulting mixture is heated in a 60 °C oil bath for 13 h, at which time TLC analysis indicates the reaction to be complete (Notes 11, 12). Then the reaction mixture is cooled to ambient temperature, and phosphate buffer (200 mL) (Note 13) is added. Organic materials are extracted with ethyl acetate (AcOEt , 3 x 200 mL), the combined extracts are washed successively with water (3 x 200 mL) and brine (200 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through a filter paper and removal of the solvent under reduced pressure (Note 14), the palladium catalyst and ammonium salt are removed by short column chromatography on silica gel (Note 15). The eluent is concentrated under reduced pressure (Note 14) to give the crude product as a brown oil. This oil is distilled twice under reduced pressure (74–77 °C/1.2–1.4 mmHg) to give *o*-(1,1-difluorohex-1-en-2-yl)aniline (5.63 g, 63%) (Note 16) as a pale yellow liquid that was pure enough (90–95%) for use in the next step.

B. *o'-(1,1-Difluorohex-1-en-2-yl)-p-toluenesulfonanilide*. A 100-mL, two-necked, round-bottomed flask containing *o*-(1,1-difluorohex-1-en-2-yl)aniline (4.94 g, 23.4 mmol) is equipped with a glass stopper, a Teflon-coated magnetic stirbar, and a stopcock inlet connected to the argon line. Pyridine (50 mL) (Note 17) is introduced and the solution is cooled to 0 °C. *p*-Toluenesulfonyl chloride (TsCl , 6.69 g, 35.1 mmol) (Note 18) is added, and the mixture is stirred at room temperature for 15 h. Water (5 mL) is added and the reaction mixture is stirred for 0.5 h. Water (50 mL) and ether (100 mL) are added to the mixture before 2 M aqueous HCl solution (400 mL) is introduced. Organic materials are extracted with ether (4 x 100 mL). The combined organic extracts are washed successively with water (100 mL) and brine (100 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through filter paper and removal of the solvent under reduced pressure (Note 14), a brown liquid (8.77 g) (Note 19) is obtained. This is used in the next step without further purification.

C. *3-Butyl-2-fluoro-1-tosylindole*. A 300-mL, two-necked, round-bottomed flask is equipped with a glass stopper, a Teflon-coated magnetic stirbar, and a reflux condenser connected to the argon line. The system is flame-dried and flushed with argon. The flask is charged with anhydrous

N,N-dimethylformamide (50 mL) (Note 1) and crude *o*'-(1,1-difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide (8.77 g) (Note 19). Sodium hydride (0.65 g, 27 mmol) (Note 20) is added in portions to the solution at 0 °C. After the reaction mixture is stirred at 0 °C for 30 min, the flask is placed in an 80 °C oil bath. The mixture is stirred at this temperature for 7 h, at which time TLC analysis indicates the reaction to be complete (Notes 11, 21). The reaction mixture is cooled to ambient temperature, and phosphate buffer (100 mL) (Note 13) is added. Organic materials are extracted with ethyl acetate (3 x 150 mL), and the combined extracts are washed with water (4 x 100 mL) and brine (100 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through a filter paper and removal of the solvent under reduced pressure (Note 14), the resulting brown residue is purified by column chromatography on silica gel (Note 22). The eluent containing the product is concentrated under reduced pressure (Note 14) to provide pure 3-butyl-2-fluoro-1-tosylindole as a yellow liquid (6.43 g, 80% over two steps) (Note 23).

2. Notes

1. Anhydrous tetrahydrofuran (THF) and *N,N*-dimethylformamide (DMF) (organic synthesis grade) were purchased from Kanto Chemical Co., Inc. and used as supplied. The checkers used anhydrous THF dried by distillation over Mg-anthracene, and DMF (Fluka) that was dried by storing over molecular sieves (3 Å) and subsequent distillation under reduced pressure.

2. Trifluoroethyl *p*-toluenesulfonate (Guaranteed Reagent grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers purchased this compound from Lancaster.

3. Butyllithium (ca. 1.6 M solution in hexane, organic synthesis grade) was purchased from Kanto Chemical Co., Inc. and used as supplied. The checkers purchased BuLi (1.64 M in hexanes) from Fischer Science.

4. The submitters introduced the butyllithium via syringe, adding the solution along the wall of the reaction flask that was cooled by a dry ice-acetone bath.

5. Tributylborane (1.0 M solution in tetrahydrofuran) was purchased from Aldrich Chemical Company, Inc. and used as supplied.

6. Anhydrous trimethylamine oxide was prepared by sublimation of trimethylamine oxide dihydrate under reduced pressure (150 °C, 2.0 mmHg). Trimethylamine oxide dihydrate (Guaranteed Reagent grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. The checkers used anhydrous

trimethylamine oxide purchased from Aldrich.

7. Triphenylphosphine (Extra Pure grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and recrystallized from methanol prior to use. The checkers used triphenylphosphine (Aldrich) recrystallized from acetone prior to use.

8. The palladium catalyst was prepared from palladium(II) diacetate and dibenzylideneacetone according to the literature method.²

9. *o*-Iodoaniline (Extra Pure grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers used the commercial sample purchased from Acros as received.

10. Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers purchased the solution of this reagent from Aldrich.

11. Silica gel TLC plates (60F₂₅₄) were purchased from Merck Ltd. Japan, and visualized with 3% aqueous KMnO₄.

12. The R_f value of iodoaniline was 0.30 (ethyl acetate:hexane (1:5)); the product possessed an R_f = 0.42 in this solvent system. The submitters reported that the reaction was complete after only 6 h.

13. Phosphate buffer (pH 7, 1 L) was prepared by dissolving KH₂PO₄ 9.1 g and Na₂HPO₄·12H₂O (47.7 g) in distilled water.

14. Rotary evaporation was conducted at 100 mmHg in a 40 °C water bath.

15. Short column chromatography was performed by using a 3.5-cm x 40-cm column packed with 250 mL of silica gel (Fuji Silysia Chemical Ltd., PSQ100B, >100 μm). The product was eluted with 500 mL of ethyl acetate:hexane (1:5). The checkers used silica gel purchased from E. Merck, Darmstadt (230–400 mesh).

16. *o*-(1,1-Difluorohex-1-en-2-yl)aniline has the following physical properties: R_f = 0.42 (ethyl acetate:hexane (1:5)); ¹H NMR (300 MHz, CDCl₃) δ: 0.84–0.89 (m, 3 H), 1.30–1.35 (m, 4 H), 2.24–2.32 (m, 2 H), 3.59 (br. s, 2 H), 6.70–6.77 (m, 2 H), 6.99 (dd, 1 H, *J* = 1.6, 7.6 Hz), 7.11 (ddd, 1 H, *J* = 1.6, 7.5, 7.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ: 13.8, 22.3, 27.7, 29.8 (dd, *J* = 2, 3 Hz), 89.0 (dd, *J* = 17, 22 Hz), 115.6, 118.4, 119.1 (dd, *J* = 1, 4 Hz), 128.9, 130.4 (dd, *J* = 2, 3 Hz), 144.2 (dd, *J* = 1, 3 Hz), 152.8 (dd, *J* = 287, 288 Hz); ¹⁹F NMR (282 MHz, CDCl₃/CFCl₃) δ: –89.2 (d, 1 F, *J* = 43 Hz), –93.2 (d, 1 F, *J* = 43 Hz); IR (KAP) 3475, 3385, 2958, 2930, 2862, 1737, 1617, 1496, 1232 cm^{–1}; MS (70 eV) *m/z* (rel intensity) 211 (M⁺; 80), 168 (98), 148 (100); Anal. Calcd for C₁₂H₁₅NF₂: C, 68.23; H, 7.16; N, 6.63. Found: C, 66.95; H, 7.86; N, 5.78.

17. Pyridine (JIS special grade) was purchased from Kokusan

Chemical Works, Ltd. and used as supplied. The checkers used pyridine (E. Merck, Darmstadt) distilled over KOH prior to use.

18. *p*-Toluenesulfonyl chloride (Extra Pure grade) was purchased from Kanto Chemical Co., Inc. and recrystallized from toluene prior to use. The checkers used tosyl chloride as received from Aldrich.

19. An analytically pure sample of the toluenesulfonanilide can be isolated by column chromatography on silica gel (Fuji Silysia Chemical Ltd., PSQ100B, >100 μm). The product was eluted with ethyl acetate:hexane (1:5) and the eluent was concentrated with a rotary evaporator (Note 14) to give *o'*-(1,1-difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide as a white powder. The product exhibits the following physical properties: R_f = 0.31 (ethyl acetate:hexane (1:5)) (Note 11); ^1H NMR (400 MHz, CDCl_3) δ : 0.79 (t, 3 H, J = 7.1 Hz), 1.05–1.23 (m, 4 H), 1.98 (br. s, 2 H), 2.35 (s, 3 H), 6.52 (s, 1 H), 6.98–7.06 (m, 2 H), 7.19–7.27 (m, 3 H), 7.60 (d, 1 H, J = 7.9 Hz), 7.68 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 13.6, 21.5, 22.2, 28.0, 29.4, 88.0 (dd, J = 16, 23 Hz), 119.7, 124.1 (d, J = 4 Hz), 124.3, 127.2, 129.1, 129.7, 130.6, 135.0, 136.4, 144.1, 153.0 (dd, J = 288, 291 Hz); ^{19}F NMR (282 MHz, $\text{CDCl}_3/\text{CFCl}_3$) δ : -86.9 (d, 1 F, J = 39 Hz), -90.3 (d, 1 F, J = 41 Hz); IR (KAP) 3274, 2958, 1742, 1494, 1401, 1339, 1247, 1167, 1092, 920, 666 cm^{-1} ; MS (70 eV) m/z (rel intensity) 365 (M^+ ; 0.5), 210 (100), 148 (62); HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2\text{F}_2\text{SNa}$ 388.11533 ($\text{M}^+ + \text{Na}$); found 388.11525.

20. The checkers used pure NaH by removing the mineral oil from the commercial sample (Aldrich) with pentane (three washings). The submitters used sodium hydride (NaH) in mineral oil (1.06 g, 60% dispersion in mineral oil, 27 mmol, organic synthesis grade) purchased from Kanto Chemical Co., Inc. without further purification.

21. The product possessed an R_f = 0.39 (ethyl acetate:hexane (1:5)).

22. Column chromatography was performed by using a 3-cm x 50-cm column packed with 300 mL of silica gel (Fuji Silysia Chemical Ltd., PSQ100B, >100 μm). The product was eluted with ethyl acetate:hexane (1:10). After collection of 200 mL of eluent, 50 mL-fractions were collected. The KMnO_4 -active product was eluted in the fractions 6–11 (Note 11). The checkers used silica purchased from E. Merck, Darmstadt (230–400 mesh).

23. 3-Butyl-2-fluoro-1-tosylindole exhibits the following physical properties: ^1H NMR (400 MHz, CDCl_3) δ : 0.84 (t, 3 H, J = 7.3 Hz), 1.16–1.25 (m, 2 H), 1.48–1.56 (m, 2 H), 2.33 (s, 3 H), 2.51 (dt, 2 H, J = 0.8, 7.4 Hz), 7.19 (d, 2 H, J = 8.0 Hz), 7.23 (ddd, 1 H, J = 1.1, 7.6, 7.6 Hz), 7.25–7.29 (m, 1 H), 7.33 (d, 1 H, J = 7.1 Hz), 7.71 (d, 2 H, J = 8.3 Hz), 8.07 (d, 1 H, J = 8.1 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 13.7, 21.3 (d, J = 2

(Hz), 21.6, 22.1, 30.5 (d, $J = 2$ Hz), 99.7 (d, $J = 11$ Hz), 114.4, 118.9 (d, $J = 7$ Hz), 123.9, 124.0 (d, $J = 4$ Hz), 126.8, 128.1 (d, $J = 6$ Hz), 129.8, 130.6, 134.7, 145.2, 147.4 (d, $J = 277$ Hz); ^{19}F NMR (282 MHz, $\text{CDCl}_3/\text{CFCl}_3$) δ : -132.8; IR (KAP) 2957, 2931, 2861, 1659, 1453, 1393, 1190, 1179, 746, 689, 663 cm^{-1} ; MS (70 eV) m/z (rel intensity) 345 (M^+ ; 91), 190 (100), 148 (71); HRMS calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2\text{FSNa}$ 368.10910 ($\text{M}^+ + \text{Na}$); found 368.10906; Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2\text{FS}$: C, 66.06; H, 5.84; N, 4.05. Found: C, 65.97; H, 5.90; N, 4.10.

Waste Disposal Information

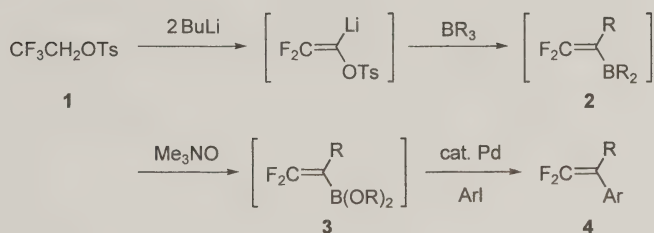
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Synthetic methods for the preparation of 2-fluoroindoles have been limited to difluorination of indole derivatives followed by elimination^{3a,b} and electrophilic fluorination of stannylindoles.^{3c} The procedures described herein illustrate an efficient construction of 2-fluoroindoles via intramolecular substitution of the vinylic fluorine in β,β -difluorostyrenes bearing an *ortho*-amido substituent.⁴ This reaction can be classified as a 5-*endo-trig* ring closure, a disfavored process according to Baldwin's rules.⁵⁻⁸ While having only rarely been observed in synthetic chemistry,⁶ the nucleophilic 5-*endo-trig* cyclization was successfully achieved by taking advantage of the unique properties of fluorine: (i) the highly polarized difluorovinylidene double bond (^{13}C NMR: ca. 150 ppm and 90 ppm for $\text{CF}_2=\text{C}$) aids initial ring formation by electrostatic attraction between the CF_2 carbon and the internal nucleophile, and (ii) the successive elimination of the fluoride ion suppresses the reverse ring opening, thus functioning as a "lock".⁴

Difluorostyrene derivatives **4** including *o*-(2,2-difluorovinyl)anilines are easily prepared by using a one-pot sequence as outlined below.^{9a,c} The sequence comprises the following two processes starting from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**): (i) a boron-mediated alkylation via 1,2-migration, leading to 2,2-difluorovinylboranes **2** and (ii) subsequent palladium-catalyzed coupling reaction with aryl iodides via 2,2-difluorovinylboronates **3**, which affords difluorostyrenes **4** in good yield.

The substituent R at the vinylic position of **4** is derived from a trialkylborane (BR₃), which is readily generated by hydroboration of the corresponding alkene. The selective oxidation of boron–alkyl bonds with trimethylamine oxide prevents the coupling reaction of B–alkyl groups in **2**.

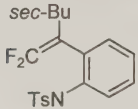
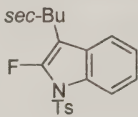
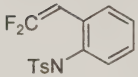
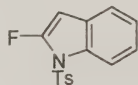
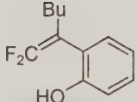
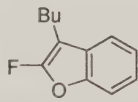
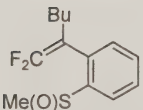
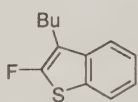
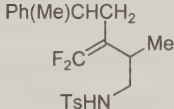
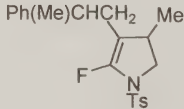
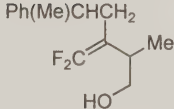
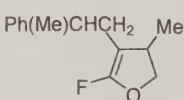
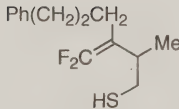
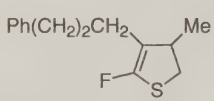


Another vinyl-selective coupling reaction of **2** with aryl iodides is accomplished via the transmetalation to 2,2-difluorovinylcopper species by adding cuprous iodide.^{4a,9b,c} β,β-Difluorostyrenes **4** (R = H) without a vinylic substituent can also be prepared via 2,2-difluorovinylzirconocene from **1**.¹⁰

After tosylation of *o*-(2,2-difluorovinyl)anilines, treatment of the obtained sulfonanilides with 1.1 equiv of NaH in DMF promotes the normally “disfavored” 5-*endo-trig* cyclization to afford the corresponding 2-fluoroindoles in high yield. High-dilution conditions are not required in this ring closure.

This methodology for constructing five-membered rings is widely applicable to the cyclization of (i) β,β-difluorostyrene derivatives and (ii) 1,1-difluoro-1-butene derivatives bearing a nucleophilic nitrogen, oxygen, or sulfur atom at the *ortho* or the homoallylic position, respectively. Under similar conditions, these substrates undergo cyclization to afford ring-fluorinated heterocycles such as pyrrolines, furans, and thiophenes in high yield as shown in the Table. Five-membered carbocycles bearing a fluorine on the ring can also be obtained by this method.^{4a,11} Moreover, six-membered ring-fluorinated heterocyclic and carbocyclic compounds can be provided in line with the “intramolecular substitution” concept.^{11b,12}

Table. Nucleophilic 5-*endo-trig*-Cyclization of 1,1-Difluoro-1-alkenes

Substrate	Product	Conditions ^a	Yield
		80 °C, 5 h	81%
		70 °C, 23 h	73%
		60 °C, 2 h	80%
		reflux, 3 h ^b	82%
		90 °C, 4 d	80%
		90 °C, 7 h	67%
		90 °C, 4 h	76%

a. NaH (1.1–1.2 equiv), DMF. b. (i) (CF₃CO)₂O (3 equiv), NEt₃ (3 equiv), CH₂Cl₂, 0 °C, 0.5 h. (ii) K₂CO₃ (6 equiv), MeOH, 0 °C–rt, 1 h then reflux.

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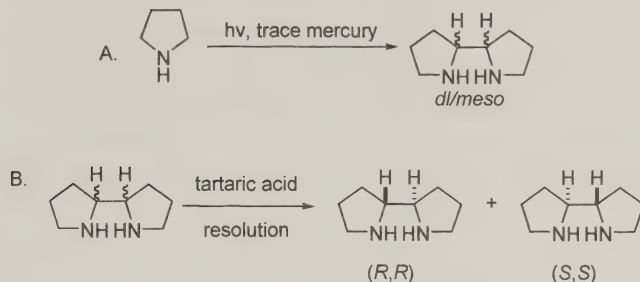
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

- o*-(1,1-Difluorohex-1-en-2-yl)aniline: Benzenamine, 2-[1-(difluoromethylene)pentyl]-; (134810-59-6)
- o*'-(1,1-Difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide: Benzenesulfonamide, *N*-[2-[1-(difluoromethylene)pentyl]phenyl]-4-methyl-; (195734-33-9)
- 3-Butyl-2-fluoro-1-tosylindole: 1*H*-Indole, 3-butyl-2-fluoro-1-[(4-methylphenyl)sulfonyl]-; (195734-36-2)
- 2,2,2-Trifluoroethyl *p*-toluenesulfonate: Ethanol, 2,2,2-trifluoro-, 4-methylbenzenesulfonate; (433-06-7)
- Trimethylamine oxide: Methanamine, *N,N*-dimethyl-, *N*-oxide; (1184-78-7)
- Tetrabutylammonium fluoride: 1-Butanaminium, *N,N,N*-tributyl-, fluoride; (429-41-4)
- o*-Iodoaniline: Benzenamine, 2-iodo-; (615-43-0)
- Triphenylphosphine: Phosphine, triphenyl-; (603-35-0)
- Tris(dibenzylideneacetone)dipalladium(0)-chloroform (1/1): Palladium, tris[μ -[(1,2- η :4,5- η)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-, compound with trichloromethane (1:1); (52522-40-4)

**(*R,R*)-2,2'-BISPYRROLIDINE and (*S,S*)-2,2'-BISPYRROLIDINE:
USEFUL LIGANDS FOR ASYMMETRIC SYNTHESIS**



Submitted by Scott E. Denmark, Jiping Fu and Michael J. Lawler.¹

Checked by Sandra Lee, Elliott Huntsman and Edward J.J. Grabowski.

Caution! This procedure should be carried out in a well-ventilated hood because of the stench of pyrrolidine and 2,2'-bispyrrolidine. The hood doors should be covered with an opaque sheet to shield the UV light.

1. Procedure

A. (*R*,R**) and (*R*,S**)-2,2'-Bispyrrolidine.^{2,3} A three-necked, 500-mL flask equipped with three quartz refluxing columns and three water condensers (Figure 1) is charged with pyrrolidine (160 mL) and a drop of mercury (Notes 1 and 2). The water condensers are equipped with gas inlets connected to a single nitrogen source leading to an oil bubbler. The flask is placed in a Rayonet Photoreactor fitted with 14 x 8 Watt low pressure Hg lamps (254 nm). The reaction mixture is heated to reflux with a heating mantle. The lamps are turned on, after which the mixture is heated at reflux for 7 days. After the lamps are turned off, the system is allowed to cool to room temperature (Note 2). The liquid is then carefully decanted to a distillation flask and the mercury is recovered. Unreacted pyrrolidine and side products are removed by distillation at atmospheric pressure (Note 3). The residue is distilled to provide 67.6 g (50%) of a mixture of (*R*,R**) and (*R*,S**)-2,2'-bispyrrolidine as a clear, light yellow liquid (bp 79–81 °C at 3.0 mmHg) (Note 4). The product is of sufficient purity to be used in the resolution step (Note 5).

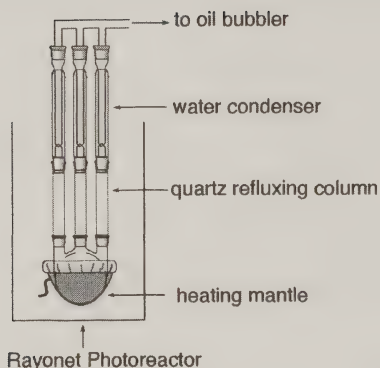


Figure 1. Apparatus for photodimerization of pyrrolidine.

B. Resolution of 2,2'-Bispyrrolidine^{3,4}

1. *Preparation of (R,R)-2,2'-bispyrrolidine•(L)-tartrate.* To a solution of a 1/1 mixture of *d,l*- and *meso*-2,2'-bispyrrolidine (67.0 g, 479 mmol) in H₂O (240 mL) is added (L)-(+)-tartaric acid (36.0 g, 240 mmol, 0.5 equiv) and acetic acid (27.4 mL, 479 mmol, 1.0 equiv) (Note 6). The mixture is heated to 90 °C and the homogenous solution is allowed to cool to room temperature slowly before it is placed in an ice bath. After the solid precipitates (Note 7), the mixture is kept in an ice bath for another 2 h. The precipitate is then filtered and is washed with ice-cold water (20 mL). The mother liquor is saved for the recovery of the (*S,S*)-2,2'-bispyrrolidine. The collected solid is dried under high vacuum (0.5 mmHg) at 80 °C for 2 h to give 31.6 g of a light yellow powder. This solid is dissolved in hot water (90 mL) and the solution is allowed to cool slowly to room temperature before it is placed in an ice bath for 1 h. The precipitate is filtered and the solid is washed with ice-cold water (10 mL). The solid is dried under high vacuum (0.5 mmHg) at 80 °C for 2 h to give 23.0 g of white crystals. This recrystallization process is repeated using water (50 mL) to give 21.4 g (62% based on isomer content) of (*R,R*)-2,2'-bispyrrolidine•(*L*)-tartrate as white prismatic crystals (Note 8).

2. *Preparation of (R,R)-2,2'-Bispyrrolidine.* To a mixture of the tartrate salt (9.1 g) in water (15 mL) at 0 °C are added KOH (20 g) pellets (Note 9). The mixture is then stirred at 0 °C for 10 min before diethyl ether (80 mL) is added, whereupon the solution is stirred at 0 °C for another 30 min. The

aqueous layer is then separated and extracted with diethyl ether (6 x 50 mL) (Note 10). The diethyl ether extracts are combined, dried (K_2CO_3) and then are concentrated under vacuum (Note 11). The residue is transferred to a dry 25-mL, round-bottomed flask. To this is added a small piece of sodium (Note 12) and the mixture is stirred at room temperature under nitrogen for 30 min. The residue is distilled under vacuum to give 3.61 g (83%) of (*R,R*)-2,2'-bispyrrolidine as a clear colorless oil (bp 97–98 °C at 8.0 mmHg) (Note 13). The enantiomeric purity of product is determined by CSP-SFC and CSP-HPLC analysis of the corresponding dibenzoyl amide derivative (Note 14).

3. *Preparation of (S,S)-2,2'-bispyrrolidine•(D)-tartrate.* The mother liquor from initial resolution is cooled to 0 °C and KOH pellets (80 g) are added slowly. The mixture is stirred vigorously at 0 °C for 10 min (Note 15). To this solution is added diethyl ether (500 mL) and the mixture is stirred at room temperature for 20 min. The aqueous layer is separated and then is extracted with diethyl ether (4 x 500 mL). The diethyl ether extracts are combined, dried (K_2CO_3), and then are concentrated under vacuum to give 48.4 g of a yellow oil. The oil is dissolved in H_2O (150 mL), then (D)-(-)-tartaric acid (34.5 g, 230 mmol) and acetic acid (27.0 mL, 473 mmol) are added (Note 16). The mixture is heated to 90 °C and the homogenous solution is allowed to cool to room temperature slowly before it is cooled in an ice bath. After the solid precipitates, the mixture is kept in an ice bath for another 2 h. The precipitate is filtered and the solid is washed with ice-cold water (10 mL), and then is dried under high vacuum (0.5 mmHg) at 80 °C for 2 h to give 23.5 g of a light-yellow powder. The solid is dissolved in hot water (60 mL) and the solution is allowed to cool slowly to room temperature before it is placed in an ice bath for another 2 h. The precipitate is filtered, washed with 10 mL of ice-cold water, and dried under high vacuum (0.5 mmHg) at 80 °C for 2 h to give 20.16 g of white prismatic crystals. This recrystallization process is repeated using water (55 mL) to give 18.4 g (55% based on isomer content) of (*S,S*)-2,2'-bispyrrolidine•(D)-(-)-tartrate as white prismatic crystals (Note 17).

4. *Preparation of (S,S)-2,2'-Bispyrrolidine.* To a solution of the tartrate salt (9.3 g) in water (15 mL) at 0 °C are added KOH pellets (20 g). The mixture is stirred at 0 °C for 10 min before diethyl ether (80 mL) is added, whereupon it is stirred at 0 °C for another 30 min. The aqueous layer is separated and then is extracted with diethyl ether (6 x 50 mL). The diethyl ether extracts are combined, dried (K_2CO_3) and then are concentrated *in vacuo* (Note 11). The residue is then transferred to a dry 25-mL, round-

bottomed flask. To this is added a piece of sodium (Note 12) and the mixture is stirred at room temperature under nitrogen for 30 min. The residue is then distilled under vacuum to give 3.51 g (80%) of (*S,S*)-2,2'-bispyrrolidine as a clear, colorless oil (bp 97–98 °C at 8.0 mmHg) (Note 18). The enantiomeric purity of product is determined by CSP-SFC and CSP-HPLC analysis of corresponding dibenzoyl amide derivative (Note 19).

2. Notes

1. The three quartz-refluxing columns are 34 cm long and 4.0 cm in diameter. All joints are well sealed with high vacuum grease to avoid leakage. Pyrrolidine (99 %) was purchased from Aldrich Chemical Company, Inc., and was used without further purification.

Variables that are difficult to control relative to the photolysis include the age and actual power of the Hg lamps, the actual length of the quartz tubes receiving the UV light and the rate of reflux. All affect the overall rate of photolysis. The checkers found it convenient to follow the progress of the photolysis by periodically sampling the reaction and analyzing it by ¹³C-NMR spectroscopy in CDCl₃. The peak heights for the methylene groups for pyrrolidine (47.1 ppm) and the bis-pyrrolidines (47.0 and 46.6) were used as measures of the relative ratios of these species. When the pyrrolidine is almost consumed in the photolysis, the reflux ceases. The submitters were able to recover ~50% of the bis-pyrrolidines after distillation following a seven-day photolysis (See Note 5). The checkers achieved the following results: 39% in seven days; 60% in nine days; 72% in 11.4 days and 60% in five days at half-scale.

2. The crude reaction mixture can be analyzed by ¹H NMR. The ratio of starting material to products can be estimated from the NMR spectrum.

3. The distillate contains 46.6 g of colorless liquid.

4. The distillation should be done carefully to avoid solidification of the diamine in the condenser.

5. The crude material (67.6 g, approximately 50% based on the pyrrolidine charged) contains a ca. 1/1 mixture of *d,l* and *meso* isomers: ¹H NMR (500 MHz, CDCl₃) δ: 1.32–1.46 (m, 2 H), 1.61–1.92 (m, 8 H), 2.82–2.98 (m, 6 H). The checkers obtained 52.6 g from the seven-day photolysis; 81.0 g from the nine day photolysis; 97.0 g from the 11.4 day photolysis and 41.5 g from the five day photolysis at half-scale.

6. L-(+)-Tartaric acid (99% GLC) was purchased from Aldrich Chemical Company, Inc., and was used without further purification. Acetic

acid (glacial) was purchased from Fisher Scientific Company and was used without further purification. In completing the checking of this procedure, the subsequent reactions were scaled to reflect the quantity of bispyrrolidines obtained in the distillations. The reactions checked at the yields indicated.

7. The initial formation of crystals may take up to 16 h. The process can be facilitated by stirring the mixture with glass rod or by addition of small amount of seed crystals.

8. The analytical data for (*R,R*)-2,2'-bispyrrolidine•(L)-tartrate are as follows:⁴ mp 212–216 °C; ¹H NMR (500 MHz, D₂O/DSS) δ: 1.88–1.98 (m, 2 H), 2.08–2.28 (m, 4 H), 2.40–2.48 (m, 2 H), 3.51–3.55 (m, 4 H), 3.92–4.00 (m, 2 H), 4.43 (s, 2 H), 4.86 (br, 6 H); ¹³C NMR (126 MHz, D₂O) δ: 25.5, 31.0, 49.1, 63.2, 76.6, 181.4; IR (KBr) cm⁻¹: 3220, 2717, 2516, 1693, 1612, 1583, 1450, 1386, 1321, 1124, 1072, 709; [α]_D²⁴ +17.9 (*c* = 1.00, H₂O); Anal. Calcd for C₁₂H₂₂N₂O₆: C, 49.65; H, 7.64, N, 9.65. Found: C, 49.80; H, 7.63; N, 9.65. The checkers noted slight chemical shift variations in the NMR spectra of this material, and attribute these to slight differences in concentration and apparent pH in the different samples.

9. Potassium hydroxide (87.7%) was purchased from Fisher Scientific Company and was used without further purification.

10. Diethyl ether was purchased from Mallinckrodt Inc. and was used without purification.

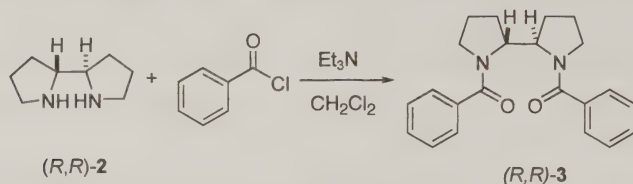
11. The water bath is kept at 0 °C to avoid loss of (*R,R*)-2,2'-bispyrrolidine.

12. The piece of sodium is about 0.5 cm³ and it is washed with hexane before use. After distillation, the sodium was destroyed by the careful addition of isopropyl alcohol.

13. The analytical data for (*R,R*)-2,2'-bispyrrolidine are as follows:^{3,4} ¹H NMR (500 MHz, CDCl₃) δ: 1.31–1.38 (m, 2 H), 1.65–1.84 (m, 6 H), 2.06 (br, 2 H), 2.82–2.97 (m, 6 H); ¹³C NMR (126 MHz, CDCl₃) δ: 25.4, 29.0, 46.4, 63.8; IR (KBr) cm⁻¹: 3270, 2956, 2867, 1282, 1118, 1076; MS (FAB) (*m/z*): 141; HRMS (*m/z*) C₈H₁₇N₂ (M+H): Calc.: 141.1386; Found: 141.1375; [α]_D²⁴ -14.91 (*c* = 1.03, MeOH); Anal. Calcd for C₈H₁₆N: C, 68.52; H, 11.50, N, 19.98. Found: C, 68.38; H, 11.64; N, 19.92. The free diamine is extremely hygroscopic, oxygen sensitive and absorbs CO₂ rapidly in air.

14. Procedure for derivatization is as follows (eq 1)^{3,4}: To a solution of (*R,R*)-2 (140 mg, 1.0 mmol) in 1.0 mL of methylene chloride (purchased from Fisher Scientific Company and distilled from P₂O₅) at 0 °C is added triethylamine (278 mL, 2.0 mmol, 2.0 equiv, purchased from Aldrich

Chemical Company, Inc., and distilled from CaH_2) and benzoyl chloride (232 mL, 2.0 mmol, 2.0 equiv, purchased from Aldrich Chemical Company, Inc., and distilled before use). The mixture is stirred at room temperature for



4 h and then EtOAc (50 mL) and H_2O (10 mL) are added. The aqueous layer is separated and then is extracted with EtOAc (3 x 15 mL). The organic layers are combined, washed with 15 mL of saturated, aqueous sodium bicarbonate solution, dried over Na_2SO_4 and then concentrated under vacuum. The residue is purified by column chromatography (SiO_2 , hexane/*i*-PrOH, 6/1) to give 295 mg (85%) of (R,R)-3 as a white solid. The analytical data for (R,R)-3 are as follows:⁴ ^1H NMR (500 MHz, CDCl_3) δ : 1.76–2.05 (m, 6 H) 2.20–2.28 (m, 2 H), 3.19 (dt, $J = 10.3, 7.8$, 2 H), 3.79 (ddd, $J = 10.5, 8.8, 5.1$, 2 H), 4.59–4.64 (m, 2 H), 7.22–7.36 (m, 6 H), 7.38–7.42 (m, 4 H); ^{13}C NMR (126 MHz, CDCl_3) δ : 24.1, 28.2, 49.1, 58.8, 127.1, 128.2, 129.5, 137.2, 164.5; IR (CHCl_3) cm^{-1} : 2997, 2881, 1624, 1576, 1427, 700; MS (EI, 70 eV): 348, 175, 174, 105; HRMS (m/z): Calc. $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$): 349.1911; Found: 349.1900; Supercritical Fluid Chromatography: t_R (R,R)-3 2.86 min (100 %); t_R (S,S)-3 3.26 min (0 %) (Chiralpak AS, 40 $^\circ\text{C}$, 150 bar, 15 % MeOH in CO_2 , 3.0 mL/min, 220 nm); HPLC: t_R (S,S)-3 8.2 min (0%); t_R (R,R)-3 13.2 min (100%) (Chiralpak AD, *i*-PrOH/hexane, 95/5, 0.7 mL/min)

15. The submitters initially used 40 g of KOH pellets for the neutralization. The checkers found that the use of 80 g was necessary to assure extraction of all of the diamine.

16. D-(–)-Tartaric acid (97% GLC) was purchased from Aldrich Chemical Company, Inc., and was used without further purification.

17. The analytical data for (S,S)-2,2'-bispyrrolidine•(D)-(–)-tartrate are as follows: mp 214–218 $^\circ\text{C}$; ^1H NMR (500 MHz, $\text{D}_2\text{O}/\text{DSS}$) δ : 1.88–1.99 (m, 2 H), 2.08–2.29 (m, 4 H), 2.41–2.49 (br, 2 H), 3.52–3.57 (m, 4 H), 3.94–4.01 (m, 2 H), 4.44 (s, 2 H), 4.84 (br, 6 H); ^{13}C NMR (126 MHz, D_2O) δ : 25.5, 31.0, 49.1, 63.16, 76.6, 181.4; IR (KBr) cm^{-1} : 3384, 3242, 2997, 2885, 2717, 2517, 1693, 1610, 1583, 1387, 1124, 1072, 710; $[\alpha]_{\text{D}}^{25} -17.7$ ($c = 1.02$, H_2O); Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_6$: C, 49.65; H, 7.64, N, 9.65. Found: C, 49.98; H, 7.43; N, 9.37. The checkers noted slight chemical shift variations

in the NMR spectra of this material, and attribute these to slight differences in concentration and apparent pH in the different samples.

18. The analytical data for (*S,S*)-2,2'-bisyrrolidine are as follows: ^1H NMR (500 MHz, CDCl_3) δ : 1.31-1.38 (m, 2 H), 1.65-1.84 (m, 6 H), 2.06 (br, 2 H), 2.82-2.97 (m, 6 H); ^{13}C NMR (126 MHz, CDCl_3) δ : 25.4, 29.0, 46.4, 63.8; IR (KBr) cm^{-1} : 3263, 2954, 2867, 2821, 1457, 1442, 1280, 1118, 1076, 892, 869; MS (FAB) (m/z) 141; HRMS (m/z) $\text{C}_8\text{H}_{17}\text{N}_2$ ($\text{M}+\text{H}$): Calc: 141.1386; Found: 141.1373; $[\alpha]_{\text{D}}^{24}$ 14.82 ($c = 1.01$, MeOH); Anal. Calcd for $\text{C}_8\text{H}_{16}\text{N}$: C, 68.52; H, 11.50, N, 19.98. Found: C, 68.45; H, 11.64; N, 19.79.

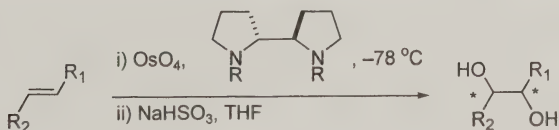
19. For the derivatization procedure see Note 14. The analytical data for (*S,S*)-**3** are as follows: ^1H NMR (500 MHz, CDCl_3) δ : 1.78–2.05 (m, 6 H), 2.20–2.27 (m, 2 H), 3.22 (dt, $J = 10.4, 7.8$, 2 H), 3.80 (ddd, $J = 10.6, 8.8, 5.1$, 2 H), 4.60–4.64 (m, 2 H), 7.23–7.33 (m, 6 H), 7.38–7.44 (m, 4 H); ^{13}C NMR (126 MHz, CDCl_3) δ : 24.3, 28.4, 49.3, 59.0, 127.4, 128.4, 129.8, 137.4, 171.2; MS (EI, 70 eV): 348, 175, 174, 105; HRMS (m/z) Calc. $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$): 349.1911; Found: 349.1917; Supercritical Fluid Chromatography: t_{R} (*R,R*)-**3** 2.86 min (0%); t_{R} (*S,S*)-**3** 3.26 min (100%) (Chiralpak AS, 40°C, 150 bar, 15% MeOH in CO_2 , 3.0 mL/min, 220 nm); HPLC: (*S,S*)-**3** t_{R} 8.2 min (100%); (*R,R*)-**3** t_{R} 13.2 min (0%) (Chiralpak AD, *i*-PrOH/hexane, 95/5, 0.7 mL/min)

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

C_2 -Symmetric chiral diamines have found extensive application as additives, auxiliaries and catalysts in asymmetric synthesis.⁵ (*R,R*)-2,2'-Bispyrrolidine, initially developed by Hirama, has been successfully applied as a ligand for osmium tetroxide in the asymmetric dihydroxylation of olefins⁶ (eq 2) and as a ligand in asymmetric hydrogenation.⁷



Several syntheses of enantiopure 2,2'-bispyrrolidine have been reported.^{4,8,9} The first synthesis described by Masamune and coworkers requires only two steps, but produces a *d,l/meso* mixture of isomers in a sluggish and irreproducible heterogeneous hydrogenation. This short synthesis arrives as the final product by direct resolution of the *d,l/meso* mixture of 2,2'-bispyrrolines.⁴ The other routes produce enantiopure 2,2'-bispyrrolines without resolution, but they require multiple-step syntheses from chiral starting materials. For example, the synthesis developed by Kotsuki and coworkers takes 11 steps from (D)-tartaric acid.⁸ Most recently, Alexakis reported a five-step synthesis of (*R,R*)-2,2'-bispyrrolidine by asymmetric addition to a chiral imine.⁹ In the procedure described herein, the *d,l/meso* mixture of 2,2'-bispyrrolidines is easily synthesized on a large scale by the photodimerization of pyrrolidine developed by Crabtree.² The previously reported resolution⁴ has been modified such that both enantiomers can be obtained.

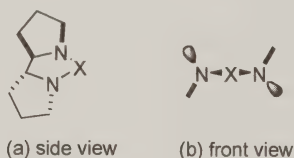
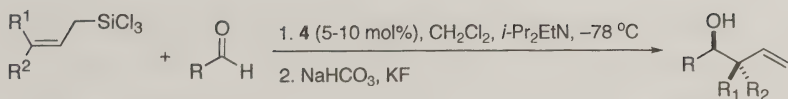
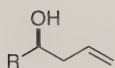
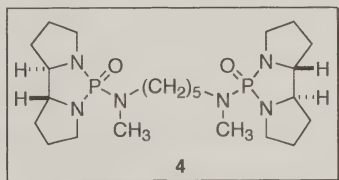


Figure 2: Stair-like structure of two pyrrolidine rings

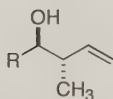
This diamine possesses very interesting structural features that impart useful characteristics as a bidentate ligand. When the two nitrogen atoms function either in a chelate or are covalently bonded to another atom, the two pyrrolidines adopted a stair-like structure, which creates a highly asymmetric environment (Figure 2). This feature was recently exploited in the development of a highly selective catalyst for asymmetric allylations (Figure 3).³ The addition of allylic trichlorosilanes to unsaturated aldehydes can be catalyzed by chiral bisphosphoramidate **4** derived from 2,2'-bispyrrolidine to give homoallylic alcohols with excellent diastereo- and enantioselectivities. Of particular note is the catalytic enantioselective construction of quaternary centers by the use of γ -disubstituted allylic silanes. The unique structural features of this diamine together with the ease of preparation bode well for further application in asymmetric synthesis.



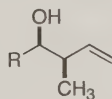
R = C₆H₅, 4-CH₃OC₆H₄, 2-naphthyl,
2-furyl, (E)-C₆H₅CH=CH,
(E)-C₆H₅CH=C(CH₃)



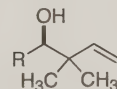
yield: 84 - 92%
ee: 80 - 88%



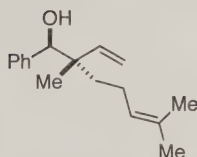
yield: 57 - 83%
anti/syn: 99/1
ee (anti): 81 - 86%



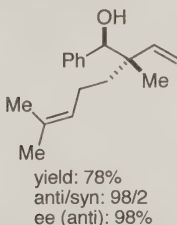
yield: 54 - 91%
syn/anti: >95/5
ee (syn): 88 - 95%



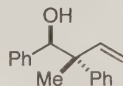
yield: 70 - 89%
ee: 88 - 96%



yield: 83%
anti/syn: 99/1
ee (anti): 94%



yield: 78%
anti/syn: 98/2
ee (anti): 98%



yield: 64%
anti/syn: 99/1
ee (anti): 93%

Figure 3. Enantioselective addition of allylic trichlorosilanes catalyzed by 2,2-bispyrrolidine-derived bisphosphoramidate **4**.

1. Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL, 61801.
2. Ferguson, R. R.; Boojamra, C. G.; Brown, S. H.; Crabtree, R. H. *Heterocycles* **1989**, 28, 121.
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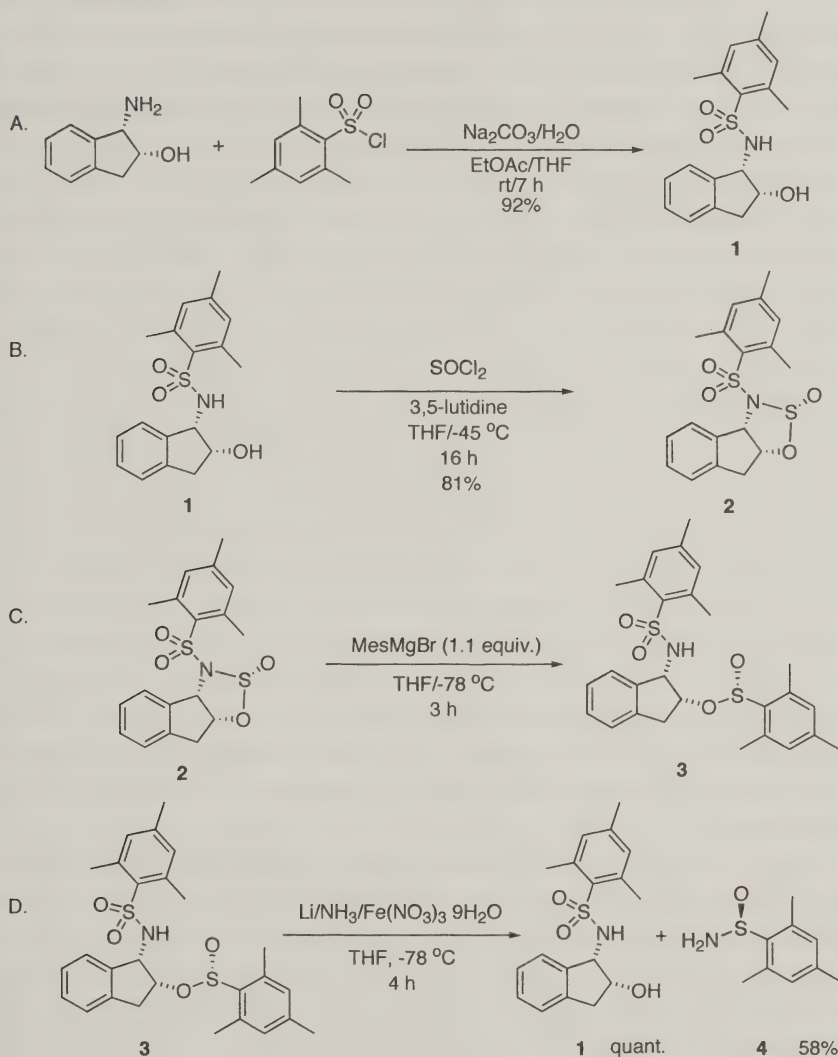
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

2,2-Bispyrrolidine; 2,2-Bipyrrolidine; (74295-58-2)
 (R,R)-2,2'-bispyrrolidine•(L)-tartrate: 2,2'-Bipyrrolidine, (2R,2'R)-, (2R,3R)-
 2,3-dihydroxybutanedioate (1:1)-; (137037-21-9)
 (S,S)-2,2'-bispyrrolidine•(D)-tartrate: 2,2'-Bipyrrolidine, [S-(R*,R*)]-, [S-
 (R*,R*)]-2,3-dihydroxybutanedioate (1:1); (136937-03-6)
 (R,R)-2,2'-Bispyrrolidine: 2,2'-Bipyrrolidine, (2R,2'R)-; (137037-20-8)
 (S,S)-2,2'-Bispyrrolidine: 2,2'-Bipyrrolidine, (2S,2'S)-; (124779-66-4)

(S)-(+)-2,4,6-TRIMETHYLBENZENESULFINAMIDE



Submitted by Tokala Ramachandar, Yongzhong Wu, Junyi Zhang, and Franklin A. Davis.¹

Checked by Shinji Harada, Riichiro Tsuji, and Masakatsu Shibasaki.

1. Procedure

A. *(1S,2R)*-(+)-*N*-(2-Hydroxyindan-1-yl)-2,4,6-trimethylbenzenesulfonamide (**1**).² A 1-L, 2-necked, round-bottomed flask equipped with a magnetic stirring bar, a 100-mL pressure-equalizing addition funnel, and a glass stopper is charged with sodium carbonate (21.34 g, 0.2 mol) and water (100 mL). The reaction mixture is stirred for 20 min. *(1S,2R)*-(-)-*cis*-1-Amino-2-indanol (15.0 g, 0.1 mol) (Note 1) is added, followed by ethyl acetate (250 mL) (Note 2). After 30 min, the addition funnel is charged with 2,4,6-trimethylbenzenesulfonyl chloride (21.3 g, 0.097 mol) (Note 1) in 50 mL of ethyl acetate and tetrahydrofuran (1:1) (Note 3), which is added dropwise to the mixture within 20 min. After the reaction mixture is stirred at ambient temperature for 7 h, water (100 mL) and ethyl acetate (200 mL) are slowly added. The resulting mixture is transferred to a 2 L separatory funnel. The reaction flask is rinsed with ethyl acetate (50 mL) and the ethyl acetate solution is added to the separatory funnel. The mixture is shaken, the phases are separated and the aqueous phase is extracted with ethyl acetate (2 × 200 mL). The combined organic phase is washed with water (100 mL), 1 N hydrochloric acid (2 × 100 mL), water (100 mL), brine (50 mL), dried over anhydrous sodium sulfate, and filtered by gravity. The solvent is removed under reduced pressure at 30 °C or lower to give a white/slightly yellow solid, which is dissolved in a 1 L Erlenmeyer flask containing ethyl acetate (150 mL). The solution is warmed to 40 °C in a water bath, and *n*-hexane (300 mL) (Note 4) is added. The solution is kept at -20 °C (Note 5) for 16 h and the resulting 30.9 g (92%) of white crystalline solid of **1** (Note 6) is collected.

B. 3-(2,4,6-Trimethylbenzenesulfonyl)-3,3a,8,8a-tetrahydro-2H-1-oxa-2λ⁴-thia-3-aza-cyclopenta[*a*]inden-2-ol (**2**).² An oven-dried, 1-L three-necked, round-bottomed flask (Note 7) equipped with a magnetic stirring bar, temperature probe, an argon inlet, and a rubber septum is charged with **1** (30.0 g, 0.090 mol). Tetrahydrofuran (180 mL) (Note 3) is added via syringe at room temperature and the solution is cooled to -45 °C (Note 8). To the colorless solution is added thionyl chloride (9.9 mL, 0.135 mol) (Note 9) *via* syringe over a 5 min period. A tetrahydrofuran (150 mL) solution containing 3,5-lutidine (25.8 mL, 0.226 mol) (Note 9) is added to the reaction mixture over 60 minutes *via* cannula at -45 °C. A white precipitate appears almost immediately. After stirring for 16 h at -45 °C, the reaction mixture is quenched at this temperature by dropwise addition of

a saturated aqueous sodium bicarbonate solution (120 mL) using a 250-mL dropping funnel. The mixture is diluted with ethyl acetate (150 mL) and warmed to room temperature with stirring. The mixture is shaken, the phases are separated and the aqueous phase is extracted with ethyl acetate (2 × 200 mL). The reaction flask is rinsed with ethyl acetate (50 mL) and the combined organic phases are transferred to a 2-L separatory funnel. The organic phase is washed with brine (100 mL), dried over anhydrous sodium sulfate, and filtered into a 500-mL round-bottomed flask. The solvent is removed under reduced pressure at 30 °C or lower. The resulting light yellow solid is stirred with *n*-heptane (250 mL) (Note 10) for 2 h affording a white precipitate. The slurry is filtered and the white cake is washed with *n*-heptane (75 mL) to give 33.0 g (yield 96.5%) of white powder. The white powder is dissolved in ethyl acetate (450 mL) in a 1-L Erlenmeyer flask at 40 °C and *n*-hexane (200 mL) is added. The solution is cooled to –20 °C (Note 6) for 16 h and filtered to give 27.5 g (81%) of a white crystalline solid **2** (Note 11).

C. (*R_S*,1*S*,2*R*)-(–)-2,4,6-Trimethylbenzenesulfinic acid 1-(2,4,6-trimethylbenzenesulfonylamino)-2-indan-2-yl ester (**3**).² An oven-dried, 1-L three-necked, round-bottomed flask (Note 7) equipped with a magnetic stirring bar, a temperature probe and an argon inlet is charged with white crystalline **2** (20.0 g, 0.053 mol). Tetrahydrofuran (400 mL) is added via syringe at room temperature and the solution is cooled to –78 °C. After 5 min, 2-mesitylmagnesium bromide (58.4 mL, 1.0 M solution in tetrahydrofuran, 0.058 mol) (Note 12) is added to the solution over a 5 min period. The slightly yellow reaction mixture is stirred at –78 °C for 3 h and quenched at this temperature by addition of a saturated sodium bicarbonate aqueous solution (100 mL) via a 250-mL dropping funnel. The mixture is diluted with ethyl acetate (150 mL), warmed to room temperature with stirring, and transferred to a 2-L separatory funnel. The mixture is shaken, the phases are separated, and the aqueous phase is extracted with ethyl acetate (2 × 200 mL). The combined organic phases are washed with brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The solvent is removed under reduced pressure at 30 °C or lower to give 26.8 g (quantitative) of a white foam, which is impure **3** (Note 13). The resulting white foam is used without further purification.

D. (*S*)-(+)-2,4,6-Trimethylphenylsulfonamide (**4**).² An oven-dried, 1-L 3-necked round-bottomed flask (Note 7) is equipped with a magnetic stirring bar. One neck of the reaction flask is fitted with an acetone-dry ice-cooled cold finger condenser bearing an argon inlet/outlet vented through a

mineral oil bubbler. Another neck is fitted with a gas inlet valve, and the third neck is fitted with a dropping funnel. The flask is cooled to $-78\text{ }^{\circ}\text{C}$ using an external acetone-dry ice bath. Ammonia (400 mL) is condensed into the flask through the gas inlet valve. The gas inlet is replaced with a stopper and crystalline iron(III) nitrate (0.1 g, 0.25 mmol) (Note 14) is added. The solution develops a brown (Note 15) color immediately. Then lithium wire (10.0 g, 1.443 mol) (Note 16) is added portion wise over 30 min and the resulting gray (Note 17) solution is stirred at $-78\text{ }^{\circ}\text{C}$ for 90 min. A solution containing the white foam **3** (20.0 g, 0.039 mol) in THF (100 mL) is added over a 30 min period via dropping funnel. The reaction mixture is stirred at this temperature for 4 h, and quenched at this temperature by addition of solid NH_4Cl (25.0 g) portion-wise over 20 min. The mixture is warmed to room temperature and the ammonia is allowed to evaporate to give a dark solid residue, to which is added Et_2O (200 mL). The mixture is filtered under vacuum into a 1-L round-bottomed flask. The solid residue is thoroughly washed with excess Et_2O ($2 \times 250\text{ mL}$) and the combined organic solutions are concentrated. Flash chromatography (SiO_2 , EtOAc :hexanes, 1:1) (Note 18) affords 13.3 g (100%) of chiral auxiliary **1** (product in *Part A*) and 4.95 g of crude **4**. This material is dissolved in EtOAc (30 mL) and *n*-hexane (30 mL) is added. The solution is kept at $-20\text{ }^{\circ}\text{C}$ (Note 6) for 24 h and then filtered to give 4.25 g (58%) of white crystalline **4** (Note 19 and 20).

2. Notes

1. (1*S*,2*R*)-(-)-*cis*-1-Amino-2-indanol and 2,4,6-trimethylbenzenesulfonyl chloride, were purchased from Aldrich Chemical Company, Inc.

2. The checkers purchased ethyl acetate from Wako Pure Chemical Industries, Ltd. and used it as received. The submitters purchased ethyl acetate from Fisher Scientific Company.

3. Reagent grade tetrahydrofuran was purified by passing through columns packed with activated alumina and supported copper catalyst (Glass Contour, Irvine, CA).

4. The checkers purchased *n*-hexane from Wako Pure Chemical Industries, Ltd. and used it as received. The submitters purchased *n*-hexane from Fisher Scientific Company.

5. A refrigerator having a freezer compartment at $-20\text{ }^{\circ}\text{C}$ was used.

6. Compound (+)-**1** exhibits the following physical and spectroscopic properties: mp 149–150 °C; $[\alpha]_D +17.9$ (*c* 1.09, CHCl₃); IR (KBr): 3476, 3331, 2949, 1601, 1331, 1154 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.33 (s, 3 H), 2.72 (s, 6 H), 2.91 (d, *J* = 17.0 Hz, 1 H), 3.08 (dd, *J* = 5.0, 16.5 Hz, 1 H), 4.40–4.43 (m, 1 H), 4.62 (dd, *J* = 5.0, 10.0 Hz, 1 H), 5.34 (d, *J* = 9.5 Hz, 1 H), 7.00 (s, 2 H), 7.12–7.24 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ: 20.9, 23.0, 39.4, 61.1, 72.9, 124.6, 125.3, 127.2, 128.5, 132.0, 133.7, 139.3, 139.4, 139.6, 142.6; Anal. Calcd for C₁₈H₂₁NO₃S: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.16; H, 6.38; N, 4.11.

7. All glassware was dried at 120 °C for at least 4 h and cooled to room temperature in a desiccator prior to use.

8. An acetonitrile/dry ice bath was used.

9. Thionyl chloride and 3,5-lutidine were purchased from Aldrich Chemical Company, Inc and used as received. The checkers found that 1.5 equiv of SOCl₂ is necessary to drive the reaction to completion.

10. The checkers purchased *n*-heptane from Wako Pure Chemical Industries, Ltd. and used it as received. The submitters purchased it from Fisher Scientific Company.

11. The known compound (–)-**2**³ exhibits the following physical and spectroscopic properties: mp 170–171 °C; $[\alpha]_D -2.6$ (*c* 1.0, CHCl₃), IR (KBr): 2937, 1601, 1335, 1158 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.38 (s, 3 H), 2.73 (s, 6 H), 3.42 (dd, *J* = 7.0, 18.5 Hz, 1 H), 3.57 (d, *J* = 17.5 Hz, 1 H), 5.54 (d, *J* = 6.5 Hz, 1 H), 5.85 (dt, *J* = 1.5, 7.0 Hz, 1 H), 6.59 (d, *J* = 8.0 Hz, 1 H), 7.07–7.27 (m, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.1, 23.1, 39.3, 66.2, 95.6, 124.7, 125.4, 127.8, 129.4, 131.9, 132.5, 138.41, 138.45, 140.9, 144.7.

12. 2-Mesitylmagnesium bromide (1.0 M solution in tetrahydrofuran) was purchased from Aldrich Chemical Company, Inc.

13. The submitter's report an isolated yield of 23.7 g (90%). A portion of compound **3** was purified for the purpose of characterization by flash chromatography (SiO₂, EtOAc:hexanes, 3:7) as follows: The product (approximately 0.1 g) is charged on a column (40 x 2.5 cm) of 50 g of silica gel and eluted with 200 mL of hexanes. At this point, fraction collection (25-mL fractions) begins, and elution is continued with 400 mL of 15% EtOAc-hexane until compound **3** is obtained in fractions 5-10. These fractions are concentrated by rotary evaporation (25 °C, 15 mmHg) to give 0.112 g (85%) of a white crystalline solid. The *R*_f of compound **3** is 0.57. The known compound (–)-**3**³ exhibits the following physical and spectroscopic properties: mp 145–146 °C; $[\alpha]_D -58.8$ (*c* 1.0, CHCl₃), IR

(KBr): 2970, 1602, 1332, 1154 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.25 (s, 3 H), 2.32 (s, 3 H), 2.43 (s, 6 H), 2.70 (s, 6 H), 3.08 (dd, $J = 4.5, 17.0$ Hz, 1 H), 3.16 (d, $J = 16.5$ Hz, 1 H), 4.85 (dd, $J = 4.5, 9.0$ Hz, 1 H), 4.96–4.98 (m, 1 H), 5.53 (d, $J = 9.5$ Hz, 1 H), 6.79 (s, 2 H), 6.98 (s, 2 H), 7.13–7.25 (m, 4 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 18.8, 20.9, 21.1, 23.1, 37.2, 60.2, 81.0, 124.4, 124.7, 127.4, 128.2, 130.7, 132.0, 134.2, 137.4, 137.6, 137.8, 139.3, 140.0, 142.3.

14. Iron(III) nitrate was purchased from Acros Organics, Inc. and was used as received.

15. The submitters reported that a gray color is formed.

16. Lithium wire (3.2 mm diameter in mineral oil, 99.9%, Catalog No: 220914) was purchased from Aldrich Chemical Company, Inc., and was cut into small pieces.

17. The submitter reported that a blue color is formed.

18. The product is charged on a column (60 x 7.5 cm) of 400 g of silica gel and eluted with 500 mL of hexane. At that point, fraction collection (75-mL fractions) begins, and elution is continued with 1 L of 20% EtOAc-hexane until auxiliary **1** is obtained in fractions 10-15. At this time the column is eluted with 1.5 L of 80% of EtOAc-hexane until sulfinamide **4** was obtained in fractions 15-25. The products fractions are concentrated by rotary evaporation (25 $^\circ\text{C}$, 15 mmHg). The R_f s of the two compounds are 0.51 (for chiral auxiliary **1**) and 0.24 (for **4**). The resulting chiral auxiliary **1** was obtained in 9.2 g (69%) by submitters. Compound **1** was used without further purification in *Part B* and the purity of the recovered auxiliary was evaluated by comparison of its physical properties with an authentic sample: mp 149–150 $^\circ\text{C}$; $[\alpha]_D +17.9$ (c 1.09, CHCl_3).

19. The known compound (+)-**4**² exhibits the following physical and spectroscopic properties: mp 120–122 $^\circ\text{C}$; $[\alpha]_D + 303$ (c 0.46, CHCl_3), IR (KBr): 3287, 3103, 1601, 1450, 1062, 1027, 848 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.27 (s, 3 H), 2.59 (s, 6 H), 4.46 (brs, 2 H), 6.85 (s, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 19.1, 20.9, 130.8, 136.1, 138.7, 140.7. The enantiomeric excess (97%) was determined by using a Chiralcel OD, 4-6 x 250 mm, 10 μm ; 9:1 (hexane/*i*-PrOH), 1.0 mL/min, 250 nm; (*S*)-**4**, $r_t = 17.5$ min; the minor isomer, (*R*)-**4**, $r_t = 23.5$ min.

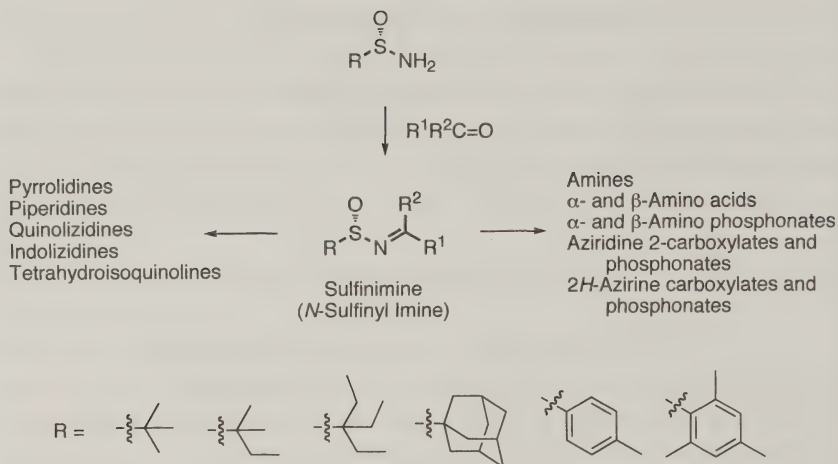
20. The submitters report the use of LiHMDS to effect the conversion of **3** to **4** on a 22.4 gram scale resulted in 11.2 g (50%) of starting material **3**, 6.8 g (46%) of the chiral auxiliary **1** and 3.8 g (46%) sulfinamide **4**. On a 1.0 g scale the LiHMDS procedure gave **4** in 70% yield.³

Waste Disposal Information

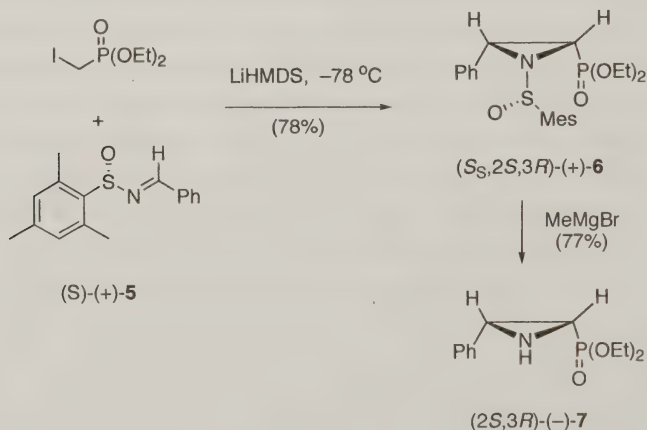
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The most direct and reliable method for the asymmetric synthesis of diverse amine derivatives is the addition of an organometallic reagent across the C-N bond of an imine having a chiral *N*-sulfinyl auxiliary.⁴ Sulfinimines (*N*-sulfinylimines) provide a general solution to the problem of addition of organometallic reagents across the C-N bond of chiral imines because the sulfinyl group activates the imine for addition, is highly stereodirecting, and easily removed in the sulfinamide product giving the enantiomerically pure amine product of known stereochemistry. Generally sulfinimines are prepared by condensation of an enantiopure (*S*)- or (*R*)-sulfinamide (RS(O)-NH₂) with an aldehyde or ketone in the presence of a weak Lewis acid dehydrating agent such as Ti(OEt)₄.⁴ For this purpose the commercially available and easily prepared *p*-toluenesulfinamide and *N*-*tert*-butanesulfinamide are generally employed. However, a useful addition to the sulfinimine protocols would be the ability to "tune" the reactivity of the sulfinimine by varying the steric and electronic properties of the *N*-sulfinyl auxiliary.⁵ The method described here for the asymmetric synthesis of (*S*)-(+)-2,4,6-trimethylphenylsulfinamide **4** is a representative general procedure for the asymmetric synthesis of structurally diverse sulfinamides developed by Senanayake and co-workers.² In this procedure *N*-sulfonyl-1,2,3-oxathiazolidines-2-oxide **2** is treated with Grignard reagents to afford the sulfenate ester **3**, which on reaction with Li/NH₃ or LiHMDS affords the corresponding enantiopure sulfinamide **4**.^{2,3} The reaction of Grignard reagents with **3** has been used to prepare enantiomerically pure sulfoxides.⁶



In the aza-Darzens reaction of (*S*)-(+)-*N*-(benzylidene)-2,4,6-trimethylphenylsulfonamide **5** (prepared using (*S*)-(+)-2,4,6-trimethylphenylsulfonamide (**4**) with lithium diethyl iodomethylphosphonate) a single diastereomeric aziridine 2-phosphonate (+)-**6** was obtained.³ Other *N*-sulfinyl auxiliaries gave mixtures of products or could not be removed with MeMgBr to give the corresponding NH-aziridine 2-phosphonate (–)-**7**. NH-Aziridine 2-phosphonates are valuable chiral building block for the synthesis of α -amino phosphonates^{3,7} and the 2*H*-azirine 3-phosphonate which are chiral imino dienophiles.⁸



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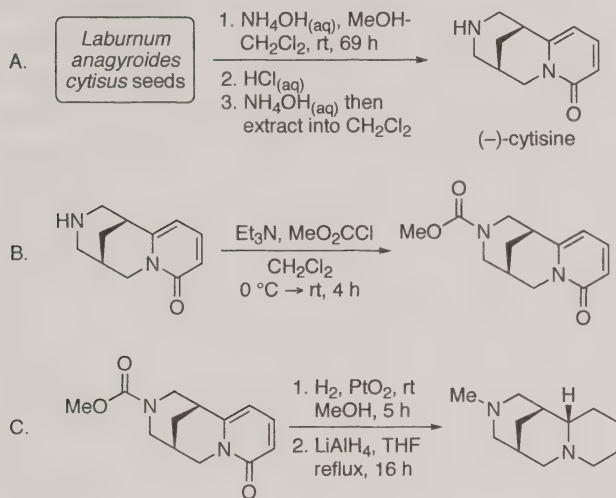
Appendix

Chemical Abstracts Nomenclature; (Registry Number)

(1*S*,2*R*)-(-)-*cis*-Aminoindanol: 1*H*-Inden-2-ol, 1-amino-2,3-dihydro-:
 (1*S*,2*R*)- (126456-43-7)
 2,4,6-Trimethylbenzenesulfonyl chloride; (773-64-8)
 (1*S*,2*R*)-(-)-*N*-(2-Hydroxy-indan-1-yl)-2,4,6-trimethyl-benzenesulfonamide:
 Benzenesulfonamide, *N*-[(1*S*,2*R*)-2,3-dihydro-2-hydroxy-1*H*-inden-1-

- yl]-2,4,6-trimethyl-; (473554-01-7)
- 3-(2,4,6-Trimethylbenzenesulfonyl)-3,3a,8,8a-tetrahydro-2*H*-1-oxa-2 λ^4 -thia-3-aza-cyclopenta[a]inden-2-ol: Indeno[1,2-d]-1,2,3-oxathiazole, 3,3a,8,8a-tetrahydro-3-[(2,4,6-trimethylphenyl)sulfonyl]-, 2-oxide, (2*R*,3*aS*,8*aR*)-; (473554-02-8)
- (*R*_S,1*S*,2*R*)-(-)-2,4,6-Trimethylbenzenesulfinic acid 1-(2,4,6-trimethylbenzenesulfonylamino)-2-indan-2-yl ester: Benzenesulfinic acid, 2,4,6-trimethyl-, (1*S*,2*R*)-2,3-dihydro-1-[[2,4,6-trimethylphenyl)sulfonyl]amino]-1*H*-inden-2-yl ester, [*S*_(S)]-; (607729-49-7)
- 2-Mesitylmagnesium bromide: Magnesium, bromo(2,4,6-trimethylphenyl)-; (2633-66-1)
- (*S*)-(+)-2,4,6-Trimethylbenzenesulfinamide: Benzenesulfinamide, 2,4,6-trimethyl-, [*S*_(S)]-; (607729-50-0)

SYNTHESIS OF (+)-(1R,2S,9S)-11-METHYL-7,11-DIAZATRICYCLO[7.3.1.0^{2,7}]TRIDECAHE, A (+)-SPARTEINE SURROGATE



Submitted by Amanda J. Dixon, Matthew J. McGrath, and Peter O'Brien.¹
 Checked by Sigrid Holle and Alois Fürstner.

1. Procedure

A. (-)-Cytisine. A 2-L, three-necked round-bottomed flask equipped with an overhead mechanical stirrer with large Teflon-coated blades (Note 1) and two glass stoppers is charged with finely ground *Laburnum anagyroides* seeds (598 g) (Notes 2 and 3), dichloromethane (837 mL), methanol (239 mL) and aqueous 25% w/v ammonium hydroxide (90 mL) (Note 4). The resulting mixture is stirred vigorously (Note 1) at room temperature. After a short induction period, a slight exotherm is observed lasting for the first ~24 h, accompanied with the formation of a thick gel (Note 1), which slowly disappears on prolonged stirring. After stirring the suspension for a total of 69 h, the mixture is filtered in three separate batches and the filter cake is washed with CH_2Cl_2 until the filtrate is colorless (Note 5). The filtrate is transferred to a 5-L separatory funnel and shaken with 3.3 M HCl (500 mL). After 2 h (Note 6), the two layers are separated and the aqueous layer is transferred to a 2-L conical flask equipped with a magnetic stirring bar. The stirred aqueous solution is basified to pH 9-10 by the

careful, portionwise addition of aqueous 25% w/v ammonium hydroxide (~150 mL) over 1 h (Note 7), followed by stirring for an additional 2 h (Note 8). The resulting solution is extracted with CH₂Cl₂ (10 × 100 mL) (Note 9). The CH₂Cl₂ extracts are combined, dried (MgSO₄), filtered and evaporated under reduced pressure to give crude (–)-cytisine (8.31 g) (Note 10) as a yellow-brown solid. The crude (–)-cytisine is purified by recrystallization (Note 11) from toluene (25-30 mL) to afford 5.25 g (0.9 % mass yield) of pure (–)-cytisine (Note 12) as a yellow-brown solid, having greater than 99.5% ee (Note 13).

B. (–)-Methyl (1*R*,9*R*)-6-Oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-diene-11-carboxylate. A flame-dried 250-mL, two-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a glass stopper and a vacuum take-off adapter attached to the argon line is charged with (–)-cytisine (5.25 g, 27.5 mmol), CH₂Cl₂ (80 mL) (Note 4) and triethylamine (4.21 mL, 30.2 mmol) (Note 14). The resulting magnetically stirred solution is immersed in an ice bath and methyl chloroformate (2.34 mL, 30.2 mmol) (Note 14) is added dropwise via syringe over 10 min at 0 °C. The resulting mixture is stirred for 1 h at 0 °C and then for 3 h at room temperature before the solvent is evaporated under reduced pressure. Ethyl acetate (EtOAc) (40 mL) is added to the residue and the solids are removed by filtration through Celite (Note 15). The filter cake is washed with EtOAc (3 × 15 mL) and the filtrate is evaporated under reduced pressure. The residue is purified by column chromatography over a short plug of silica (Note 16) with CH₂Cl₂:MeOH (9:1) as eluent. The fractions containing the product (*R_f* = 0.51; 9:1, CH₂Cl₂:MeOH) are combined and evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying (10^{–3} mbar) for 2 h to afford 6.45 g (94%) of pure cytisine methyl carbamate (Note 17) as a thick colorless oil.

C. (+)-(1*R*,2*S*,9*S*)-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane. A flame-dried, 250-mL, three-necked round-bottomed flask equipped with a magnetic stir bar, a glass stopper, and a vacuum take-off adapter that can be attached either to the argon line or to the H₂ supply is charged with cytisine methyl carbamate (6.50 g, 26.2 mmol), MeOH (100 mL) and platinum(IV) oxide (600 mg, 2.7 mmol) (Note 18). The resulting magnetically-stirred suspension is carefully evacuated and backfilled with argon (three times) before evacuating and backfilling with hydrogen (*via* hydrogen balloons attached to the two-tap adaptor). The cloudy black mixture is stirred vigorously under a hydrogen atmosphere for 5-12 h (Note 19). The solids are removed by filtration through Celite (Note 20) and the filter cake is washed

with $\text{CH}_2\text{Cl}_2\text{:MeOH}$ (9:1) (50 mL). The filtrate is evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying (10^{-3} mbar) to afford 5.93 g (90 %) of crude hydrogenation product (Note 21) as an off-white solid.

A flame-dried, 500-mL, two-necked round-bottomed flask equipped with a magnetic stir bar, a reflux condenser attached to the argon line, and a glass stopper is charged with lithium aluminium hydride (5.12 g, 134.6 mmol) and tetrahydrofuran (THF) (150 mL) (Note 22). The resulting magnetically-stirred suspension is immersed in an ice bath and a solution of the crude hydrogenation product (5.93 g, 23.5 mmol) in THF (150 mL) is added dropwise over 10 min *via* a cannula at 0 °C. The mixture is allowed to warm to room temperature and then refluxed under argon for 16 h (Note 23). After cooling to 0 °C, diethyl ether (150 mL) is added, followed by the careful, portionwise addition of solid hydrated sodium sulfate ($\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$) (17 g) (Note 22), which causes a vigorous evolution of hydrogen gas. The resulting viscous mixture is stirred for 30 min until gas evolution has ceased and the solids are removed by filtration through Celite (Note 24). The filter cake is washed with $\text{CH}_2\text{Cl}_2\text{:MeOH}$ (9:1) (150 mL) and the washings are combined, dried (Na_2SO_4), filtered and evaporated under reduced pressure to give crude diamine (3.95 g). The crude diamine is purified by Kugelrohr distillation (oven temperature 150–160 °C at 0.07 mbar) to afford 2.65 g (52% over two steps) of pure diamine (Note 25) as a colorless oil, having greater than 95% ee (Note 26).

2. Notes

1. Effective stirring is essential for the success of the isolation process. Because the reaction mixture temporarily forms a thick gel for several hours that slowly disappears, the use of a strong mechanical stirrer is required. The checkers used a mechanical stirrer with approximately 9 x 2 cm Teflon-coated blades. An effective extraction was ensured at 300 turns/min of this stirrer.

2. *Laburnum Anagyroides* seeds were purchased from Vilmorin, Division Semences d'Arbres, Route du Manoir, 49250 La Ménitré, France.

3. The seeds are ground to a fine (< 2 mm), non-uniform powder by using a standard coffee grinder. Typically, 30-50 g batches of the seeds are ground for ~30 sec. The use of coarse particles results in an inefficient extraction and/or extended extraction times.

4. Dichloromethane, methanol, toluene and 12 M hydrochloric acid (diluted with water to 3.3 M) were purchased from Aldrich and used as received. Ammonium hydroxide (25% w/v) purchased from Reininghaus was used as received.

5. The following procedure is used for the filtration process: (i) approximately one third of the stirred reaction mixture slurry is rapidly poured into a 14 cm-diameter Büchner funnel (fitted with a 12.5 cm-diameter Whatman No. 1 filter paper) attached to a 2-L Büchner flask. The filter cake is sucked dry and then washed with CH_2Cl_2 (~100-150 mL) until the filtrate runs through colorless. The filter cake is discarded. (ii) CH_2Cl_2 (150 mL) is added to the extraction mixture in the round-bottomed flask and approximately half of the remaining stirred mixture slurry is rapidly poured into the Büchner funnel/flask set-up. The filter cake is sucked dry and then washed with CH_2Cl_2 (150 mL) until the filtrate runs through colorless. The filter cake is discarded. (iii) The final portion of the reaction mixture slurry is filtered by repeating step (ii). The total volume of the filtrate at this stage is typically 1.8 L.

6. The mixture is left for 2 h to complete acidification and is periodically shaken with frequent venting to ensure good mixing. The pH is 1–2 as tested by pH paper (E. Merck, Darmstadt).

7. The basification is exothermic and a slow addition of the aqueous 25% w/v ammonium hydroxide is necessary.

8. The solution is left for at least 2 h so that a stable pH of 9-10 (pH paper, E. Merck, Darmstadt) is obtained. The solution can be left overnight at this stage without any detrimental effect on the isolated yield of (–)-cytisine.

9. If the mixture is not extracted with 10×100 mL portions of CH_2Cl_2 , lower yields of (–)-cytisine are obtained.

10. The yield of crude (–)-cytisine can vary widely (8-15 g) depending on the particular crop of the seeds that is used, but ≥ 5 g of pure (–)-cytisine is typically obtained after recrystallization from 25-30 mL of toluene.

11. For recrystallization, the crude product is dissolved in 25-30 mL of boiling toluene in a 50-mL conical flask and then allowed to cool slowly by standing overnight at room temperature. The flask is cooled at 0 °C for 1 h before collecting the crystals by filtration. The submitters report that on some occasions it is necessary to collect a second crop of crystals to ensure that >5 g of pure (–)-cytisine is obtained.

12. The properties are as follows: ^1H NMR (CDCl_3 , 300 MHz) δ : 1.94 (br s, 2 H), 2.24 (br s, 1 H), 2.32 (br s, 1 H), 2.89 (br s, 1 H), 2.97–3.13 (m, 4

H), 3.90 (dd, 1 H, $J = 15.5, 6.5$ Hz), 4.10 (d, 1 H, $J = 15.5$ Hz), 5.98 (dd, 1 H, $J = 6.8, 1.4$ Hz), 6.42 (dd, 1 H, $J = 9.1, 1.4$ Hz), 7.27 (dd, 1 H, $J = 9.1, 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75.5 MHz) δ : 26.1, 27.6, 35.3, 49.6, 52.6, 53.6, 105.1, 116.8, 138.8, 150.7, 163.6; IR (film): 1649, 1546 cm^{-1} ; $[\alpha]_{\text{D}}^{20} -59.3$ (CHCl_3 , c 0.84); mp 153–154 $^{\circ}\text{C}$; $R_f = 0.16$ (9:1, CH_2Cl_2 :MeOH).

13. The submitters determined the enantiomeric excess by conversion into *N*-benzyl cytosine and analysis by chiral HPLC: A 10-mL, one-necked round-bottomed flask equipped with a magnetic stirrer bar and reflux condenser (fitted with a rubber septum, attached to a nitrogen line) is charged with (–)-cytosine (100 mg, 0.52 mmol), benzyl bromide (0.14 mL, 1.04 mmol), potassium carbonate (380 mg, 2.6 mmol) and acetonitrile (3 mL). The resulting magnetically-stirred suspension is heated at reflux under nitrogen for 5 h. After cooling to room temperature, the solvent is evaporated under reduced pressure. Dichloromethane (10 mL) is added to the residue and the solids are removed by filtration through Celite. The filtrate is evaporated under reduced pressure and the residue is purified by column chromatography over silica with CH_2Cl_2 and then CH_2Cl_2 :MeOH (97:3) as eluent. The fractions containing the product ($R_f = 0.6$; 9:1, CH_2Cl_2 :MeOH) are combined and evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying to afford 137 mg (94%) of pure *N*-benzyl cytosine as a white solid. The properties are as follows: ^1H NMR (CDCl_3 , 400 MHz) δ : 1.77–1.94 (m, 2 H), 2.32 (dd, 1 H, $J = 11.0, 2.0$), 2.37 (br d, 1 H, $J = 11.0$), 2.40–2.48 (m, 1 H), 2.83–2.96 (m, 3 H), 3.39 (d, 1 H, $J = 14.0$), 3.46 (d, 1 H, $J = 14.0$), 3.89 (dd, 1H, $J = 15.0, 7.0$), 4.12 (d, 1 H, $J = 15.0$), 5.84 (dd, 1 H, $J = 7.0, 1.0$), 6.50 (dd, 1 H, $J = 9.0, 1.0$), 6.98–7.01 (m, 2 H), 7.17–7.23 (m, 3 H), 7.29 (dd, 1 H, $J = 9.0, 7.0$); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ : 25.9, 28.1, 35.4, 49.9, 59.9, 60.0, 61.9, 104.6, 116.5, 126.8, 128.1, 138.0, 138.5, 151.4, 163.6 (one aromatic resonance not resolved); IR (CH_2Cl_2) cm^{-1} 1650, 1560, 1545; $[\alpha]_{\text{D}}^{20} -302$ (CHCl_3 , c 0.5); mp 139–141 $^{\circ}\text{C}$; $R_f = 0.6$ (9:1 CH_2Cl_2 -MeOH). HPLC analysis using a Chiralcel-OD column with 20% 2-propanol in heptane containing 0.1% diethylamine as eluent, and a flow rate of 0.5 mL/min indicates a single peak with retention time of 18 min. HPLC analysis of the corresponding racemic *N*-benzyl cytosine affords two peaks at 18 min and 23 min corresponding to (–)- and (+)-cytosine, respectively.

14. Triethylamine was purchased from Aldrich and distilled over potassium hydroxide before use. Methyl chloroformate was purchased from Aldrich Chemical Company, Inc. and used as received. Ethyl acetate (EtOAc) was purchased from Fisher Scientific and used as received.

15. Filtration is through a 1 cm-depth of Celite in a 5 cm-diameter Büchner funnel (fitted with a 42.5 mm-diameter Whatman No. 1 filter paper) attached to a 250-mL Büchner flask.

16. Flash silica gel 60 (220-440 mesh) purchased from E. Merck, Darmstadt, is placed in a 4 cm-diameter column (8 cm-depth of silica) and eluted with ~300-400 mL of solvent.

17. The submitters reported a yield of 99%. The properties are as follows: ^1H NMR (CDCl_3 , 400 MHz) δ : 1.85–2.00 (m, 2 H), 2.42 (br s, 1 H), 3.02 (br s, 3 H), 3.41–3.60 (m, 3 H), 3.83 (dd, 1 H, $J = 15.6, 6.6$ Hz), 4.09 (d, 1 H, $J = 15.6$ Hz), 4.01–4.32 (m, 2 H), 6.02 (d, 1 H, $J = 5.6$ Hz), 6.40 (dd, 1 H, $J = 9.1, 1.5$ Hz), 7.25 (dd, 1 H, $J = 9.1, 6.5$ Hz); ^{13}C NMR (CDCl_3 , 100.6 MHz) rotamers observed, δ for major rotamer: 25.7, 27.1, 34.3, 48.9, 50.1, 51.0, 52.7, 105.6, 117.3, 138.9, 148.8, 156.1, 163.4; IR (film): 1700, 1656, 1546 cm^{-1} ; $[\alpha]_{\text{D}}^{20}$ –207.9 (CHCl_3 , c 0.47); $R_f = 0.51$ (9:1, CH_2Cl_2 :MeOH).

18. Platinum(IV) oxide (surface area ≥ 60 m^2/g , 81-83% Pt) was purchased from Heraeus and used as received.

19. The time required for the hydrogenation reaction to reach completion varies from 5-12 h (even when the same batch of platinum(IV) oxide was employed). The disappearance of starting methyl carbamate can be identified qualitatively by TLC: $R_f = 0.5$ (9:1, CH_2Cl_2 :MeOH) for methyl carbamate.

20. Filtration is through a 2-cm depth of Celite in a 5-cm diameter Büchner funnel (fitted with a 42.5 mm-diameter Whatman No. 1 filter paper) attached to a 250-mL Büchner flask.

21. The crude hydrogenation product is of sufficient purity for direct use in the next step. It can be purified by column chromatography over silica with CH_2Cl_2 :MeOH:aqueous 25% w/v ammonium hydroxide (97:2:1) as eluent. The fractions containing the product ($R_f = 0.3$; 97:2:1 CH_2Cl_2 :MeOH:aqueous 25% w/v ammonium hydroxide) are combined and evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying (10^{-3} mbar) to afford pure hydrogenation product as a white solid. The physical properties are as follows: ^1H NMR (CDCl_3 , 400 MHz) approx. 4:1 mixture of rotamers, δ : 1.52–1.67 (m, 2 H), 1.73–1.98 (m, 5 H), 2.06–2.21 (m, 1 H), 2.27–2.49 (m, 2 H), 2.77 (br d, 1 H, $J = 13.5$ Hz), 2.84 (dd, 0.85 H, $J = 13.9, 2.0$ Hz), 2.92 (br d, 0.15 H, $J = 13.9$ Hz), 2.98 (br d, 0.15 H, $J = 13.0$ Hz), 3.04 (br dt, 0.85 H, $J = 13.5, 2.1$ Hz), 3.40–3.47 (m, 1 H), 3.57 (s, 2.5 H), 3.64 (s, 0.5 H), 4.17 (d, 0.85 H, $J = 13.5$ Hz), 4.26 (br d, 0.15 H, $J = 13.0$ Hz), 4.34 (br d, 0.15 H, $J = 13.5$ Hz), 4.58

(d, 0.85 H, $J = 13.9$ Hz), 4.71 (br, 0.15 H), 4.74 (d, 0.85 H, $J = 13.5$ Hz); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ : 20.1, 27.7, 27.8, 32.7, 33.1, 33.3, 44.3, 45.8, 49.0, 52.6, 59.5, 156.1, 169.6; IR (film): 1695, 1635 cm^{-1} ; $[\alpha]_{\text{D}}^{20} -169.9$ (CHCl_3 , c 1.05); mp 118–120 $^{\circ}\text{C}$; $R_f = 0.2$ (97:2:1, CH_2Cl_2 :MeOH:aq. 25% w/v ammonium hydroxide).

22. Lithium aluminum hydride and hydrated sodium sulfate were purchased from Aldrich Chemical Company, Inc. and used as received. Tetrahydrofuran was purchased from Fisher Scientific and distilled from sodium/benzophenone ketyl under nitrogen. Diethyl ether was purchased from Fisher Scientific and used as received.

23. The reaction mixture should not be heated at reflux for more than 16 h as a lower yield of diamine is obtained.

24. Filtration is through a 2-cm depth of Celite in a 5-cm diameter Büchner funnel (fitted with a 42.5-mm diameter Whatman No. 1 filter paper) attached to a 1-L Büchner flask.

25. The submitters report a yield of 62% over two steps. A similar yield (61%) was obtained by the checkers when the reaction was performed on half-scale. The physical properties of the product are as follows: ^1H NMR (CDCl_3 , 400 MHz) δ : 1.18–1.31 (m, 2 H), 1.41–1.80 (m, 9 H), 1.85 (br d, 1 H, $J = 11.0$ Hz), 1.92 (dd, 1 H, $J = 11.5$, 3.1 Hz), 2.10 (s, 3 H), 2.08–2.13 (m, 1 H), 2.19 (ddd, 1 H, $J = 11.2$, 3.5, 1.6 Hz), 2.79–2.87 (m, 2 H), 2.92–2.98 (m, 2 H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ : 25.1, 25.7, 30.6, 30.8, 33.9, 35.2, 47.4, 56.3, 57.6, 60.4, 60.5, 66.4; IR (film): 2930 cm^{-1} ; $[\alpha]_{\text{D}}^{20} + 29.7$ ($c = 1.10$, EtOH).

26. The enantiomeric excess was determined by high resolution ^1H NMR spectroscopy (400 MHz, CDCl_3) in the presence of 3.0 equivalents of (*R*)- or (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol: A 0.12 M solution of the diamine in CDCl_3 is prepared by dissolving the diamine (46 mg, 0.24 mmol) in CDCl_3 (2.0 mL) and a 0.06 M solution of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol in CDCl_3 is prepared by dissolving (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (33 mg, 0.12 mmol) in CDCl_3 (2.0 mL). The sample for ^1H NMR spectroscopy analysis is then prepared by using 0.06 mL of the 0.12 M solution of the diamine in CDCl_3 (0.006 mmol), 0.36 mL of the 0.06 M solution of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol in CDCl_3 (0.018 mmol, 3.0 equiv.) and 0.18 mL of CDCl_3 (total volume of NMR sample ~ 0.6 mL). Key signals: ^1H NMR (CDCl_3 , 400 MHz) δ : 2.11 (s, 3 H), 2.53 (br s, 1 H), 2.66 (br s, 1 H), 2.87 (br d, 1 H, $J = 11.0$ Hz), 2.95 (br d, 1 H, $J = 11.0$ Hz). In a similar fashion, a sample for ^1H NMR spectroscopy analysis is prepared using 0.05 mL of the 0.12 M solution of the diamine in CDCl_3 (0.006

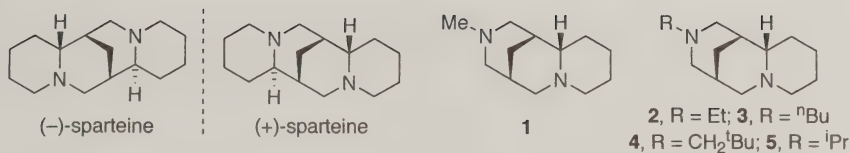
mmol), 0.30 mL of a 0.06 M solution of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol in CDCl₃ (0.018 mmol, 3.0 equiv) and 0.15 mL of CDCl₃ (total volume of NMR sample ~ 0.5 mL). Key signals: ¹H NMR (CDCl₃, 400 MHz) δ: 1.97 (s, 3 H), 2.65–2.85 (m, 2 H), 2.93 (br d, 1 H, *J* = 11.0). The absence of any signals due to the other diastereomeric complex in each of these ¹H NMR spectra indicates that the diamine is present in greater than 95% ee. (*R*)- and (*S*)-2,2,2-Trifluoro-1-(9-anthryl)ethanol were purchased from Aldrich Chemical Company, Inc. and used as received.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

(–)-Sparteine is a widely used ligand in asymmetric synthesis² but suffers from the drawback that it is only commercially available in one enantiomeric form. Diamine (+)-**1** was designed as a (+)-sparteine surrogate because it possesses most of the three-dimensional architecture of (+)-sparteine. The procedure described here is a simple, three-step synthesis of diamine (+)-**1** from *Laburnum anagyroides cytisus* seeds.^{3,4} The route has been successfully used by other research groups.^{5–7} The extraction process is a modified version of a protocol reported by Rouden, Lasne and coworkers⁸ and is a simple and high yielding alkaloid isolation. Subsequent *N*-protection (as a methyl carbamate), pyridone hydrogenation (completely diastereoselective in the sense depicted, as established by X-ray crystallography)⁴ and lithium aluminum hydride reduction furnishes diamine (+)-**1** in good overall yield. Distillation (Kugelrohr) of the diamine immediately before use is recommended (as is usual when using (–)-sparteine with organolithium reagents).⁹ Two multi-step, asymmetric syntheses of (–)-**1**¹⁰ and (+)-**1**¹¹ have also been described. Other analogues of which **2–4**^{5,12} are representative, have been prepared by using the appropriate acid chloride in the first step of the synthesis and analogue **5** was prepared by using a modified route.^{5,13} In terms of applications, we^{12,13} and others^{5,6} have found that diamine (+)-**1** is the most effective and versatile (+)-sparteine surrogate of those diamines prepared from (–)-cytisine.



A diverse range of examples that utilizes diamine (+)-**1** in asymmetric synthesis with organolithium reagents is presented in Table 1. All of the products show opposite enantioselectivity to those obtained with (-)-sparteine and a similarly high degree of enantioselection, thus demonstrating that (+)-**1** is an excellent (+)-sparteine surrogate. Lithiations and subsequent rearrangement (Entry 3) or electrophilic trapping (Entries 1-2 and 4-8), including three examples reported by other groups (Entries 6-8),^{5,6} are particularly successful. Recently, (+)-**1** was used to control the *regioselectivity* of deprotonation of an enantiomerically enriched functionalized *N*-Boc pyrrolidine used in a route to (-)-kainic acid.⁷ In a similar fashion, inter- and intramolecular carbolithiations work well (Entries 9-10).

The use of diamine (+)-**1** is not limited to organolithium-mediated processes; reactions including magnesium (Entry 1), copper (Entry 2) and palladium (Entry 3) are also successful (Table 2). The results in Tables 1 and 2 cover a wide range of mechanistic pathways and processes (namely asymmetric deprotonation and substitution, carbometallation, anhydride ring opening, dynamic thermodynamic resolution and kinetic resolution).


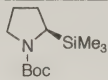
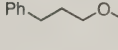
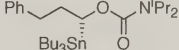


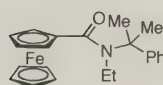
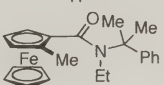
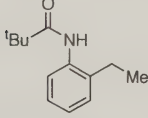
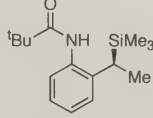


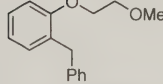
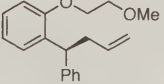
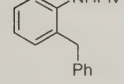
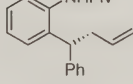
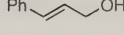
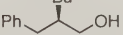
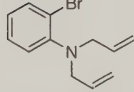
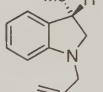
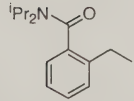
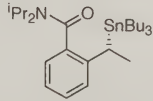
Examples where diamine (+)-**1** actually outperforms (-)-sparteine include phosphine borane lithiation (Table 1, entry 6), benzylic organolithium functionalization (Table 1, entries 7-8) and copper(II)-mediated dynamic thermodynamic resolution of racemic BINOL (Table 2, Entry 2). In recent work, we have introduced a new ligand exchange catalytic approach for asymmetric deprotonation using sub-stoichiometric amounts of (-)-sparteine and (+)-**1**. In all cases, (+)-**1** gives higher enantioselectivity than (-)-sparteine.¹⁴

In contrast, we are aware of three processes where diamine (+)-**1** is significantly inferior to (-)-sparteine. First, dynamic kinetic resolution of *N,N*-diisopropyl-*o*-ethylbenzamide gave an enantiomeric ratio of 68:32 with (+)-**1** (Table 1, entry 11) but an enantiomeric ratio of 94:6 with (-)-sparteine. Second, attempted kinetic resolution of racemic indanol using palladium(II) and molecular oxygen in the presence of (+)-**1** gave a selectivity factor (*s*) of 6.8 whereas *s* = 8.3 was obtained using (-)-sparteine (Table 2, entry 3).

Finally, the attempted dynamic thermodynamic resolution of lithiated *tert*-butylphenylphosphine borane using (+)-**1** generated a racemic adduct (95% ee with (–)-sparteine).¹² Crucial to the success of this protocol is the formation of a “voluminous precipitate” during the equilibration, and this was not observed with (+)-**1**.¹⁵

To summarize, the procedure presented here is a simple synthesis of diamine (+)-**1**. Evaluation of diamine (+)-**1** by us and others has demonstrated that it is a very good mimic of (+)-sparteine and can be employed in reactions where (–)-sparteine is a successful ligand. It thus allows access to a range of products of opposite absolute configuration to those obtained by using (–)-sparteine.

Table 1. Asymmetric Synthesis Using (+)-Sparteine Surrogate **1** and Organolithium Reagents

Entry	Substrate	Product	Yield (%)	er	Ref
1			84 ^a	95:5	3, 4, 16
2			84 ^b	96:4	3, 17
3			70 ^c	81:19	3, 12, 18
4			78 ^d	96:4	19, 20
5			58 ^e	93:7	12, 21
6			78 ^f	96:4	5, 22
7			90 ^g	96:4	6
8			89 ^h	90:10	6
9			71 ⁱ	87:13	12, 23
10			84 ^j	85:15	24, 25
11			41 ^k	68:32	21, 26

^a (i) ^sBuLi, (+)-**1**, −78 °C, Et₂O, 5 h; (ii) Me₃SiCl. ^b (i) ^sBuLi, (+)-**1**, −78 °C, Et₂O, 5 h; (ii) Bu₃SnCl.


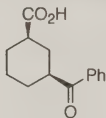
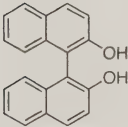
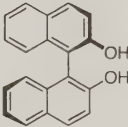


^c ^sBuLi, (+)-**1**, −78 °C, Et₂O, 5 h. ^d (i) ⁿBuLi, (+)-**1**, −78 °C, 6:1 Et₂O-toluene, 2 h; (ii) MeI.

^e ^sBuLi, Et₂O, −25 °C, 2 h; (ii) (+)-**1**, −25 °C, 45 min; (iii) −78 °C then Me₃SiCl. ^f (i) ^sBuLi, (+)-**1**, −78 °C, 3 h; (ii) Ph₂CO; (iii) HCl(aq). ^g (i) ^sBuLi, (+)-**1**, −78 °C, Et₂O; (ii) −20 °C, 1 h; (iii) −78 °C then 0.5 eq allyl tosylate; (iv) −20 °C, 1 h; (v) −78 °C then 0.5 eq allyl tosylate, warm to rt.

^h ^sBuLi, Et₂O, 0 °C, 3 h; (ii) (+)-**1**, −78 °C, 2 h; (iii) allyl bromide, warm to rt. ⁱ ⁿBuLi, (+)-**1**, 0 °C, cumene, 1 h. ^j (i) ^tBuLi, −78 °C, Et₂O-pentane, 10 min; (ii) (+)-**1**, −40 °C, 1.5 h; (iii) MeOH.

^k (i) ^sBuLi, (+)-**1**, −78 °C, pentane, 90 min; (ii) Bu₃SnCl, −78 °C, 1 h.

Table 2. Asymmetric Synthesis Using (+)-Sparteine Surrogate **1** and Magnesium, Copper and Palladium.

Entry	Substrate	Product	Yield (%)	er	Ref
1			78 ^a	89:11	12, 27
2	 racemic		86 ^b	99:1	12, 28
3	 racemic		— ^{c,d}	—	12, 29

^a PhMgCl, (+)-**1**, −78 °C, toluene, 20 h. ^b (i) CuCl, air, MeOH, (+)-**1**, rt, sonicate, 30 min; (ii) Ar, rt, sonicate, 1 h; (iii) *rac*-BINOL, CH₂Cl₂-MeOH, rt, 8 h; (iv) −25 °C, 16 h; (v) −25 °C, conc. HCl.

^c (+)-**1**, Pd(nbd)Cl₂, O₂, 3 Å MS, 60 °C, toluene, 54 h. ^d Selectivity factor for kinetic resolution, *s* = 6.8.

- Department of Chemistry, University of York, Heslington, York YO10 5DD UK.
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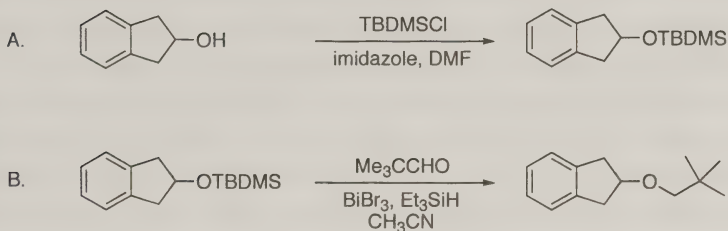
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

- (-)-Cytisine: 1,5-Methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one, 1,2,3,4,5,6-hexahydro-, (1*R*,5*S*)-; (485-35-8)
- (-)-Methyl (1*R*,9*R*)-6-Oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-diene-11-carboxylate: 1,5-Methano-2*H*-pyrido[1,2-*a*][1,5]diazocine-3(4*H*)-carboxylic acid, 1,5,6,8-tetrahydro-8-oxo-, methyl ester, (1*R*,5*R*)-; (125109-97-9)
- (+)-(1*R*,2*S*,9*S*)-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane: 1,5-Methano-2*H*-pyrido[1,2-*a*][1,5]diazocine, decahydro-3-methyl-, (1*R*,5*S*,11*aS*)-; (475301-86-1)

2-(2',2'-DIMETHYLPROPOXY)-2,3-DIHYDRO-1H-INDENE



Submitted by Joginder S. Bajwa,¹ Kapa Prasad and Oljan Repič.
 Checked by Sigrid Holle and Alois Fürstner.

1. Procedure

A. 2,3-Dihydro-2-*tert*-butyldimethysiloxy-1H-indene. A flame-dried 500-mL, four-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a pressure-equalizing dropping funnel, a nitrogen inlet, an internal thermometer and a glass stopper is charged successively under nitrogen atmosphere with 2-indanol (13.42 g, 100 mmol), imidazole (8.17 g, 120 mmol) and 60 mL of dry *N,N*-dimethylformamide (DMF) (Note 1). The mixture is stirred until a clear solution has formed (Note 2). The flask is immersed in an ice bath and a solution of *tert*-butyldimethylsilyl chloride (16.32 g, 108 mmol) in 40 mL of dry DMF (Note 3) is added over a period of 10 min at such a rate that the reaction temperature remains below 10 °C. The ice-water bath is removed, the mixture is allowed to warm to ambient temperature and stirring is continued for 45 min (Note 4). Deionized water (150 mL) is added slowly via the dropping funnel, causing a slight exotherm (Note 5), followed by the addition of 100 mL of *n*-heptane. The resulting mixture is filtered through a pad of Celite (Note 6), the organic layer is separated, and the aqueous phase is extracted with 100 mL of *n*-heptane. The combined organic phases are washed with 100 mL of water, dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation (40 °C/10 mmHg). The crude product is purified by flash chromatography on 100 g of silica gel (Note 1) packed in a 4.5 x 38 cm column. Elution with *n*-heptane (650 mL) followed by 2% ethyl acetate in *n*-heptane (about 1 L) provides 22.5 g (91 %) of 2,3-dihydro-2-*tert*-butyldimethysiloxy-1H-indene as a colorless oil (Notes 7, 8).

B. *2-(2,2-Dimethylpropoxy)-2,3-dihydro-1H-indene*. A 250-mL, flame-dried three-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a distillation head attached to a Liebig condenser, a nitrogen inlet and an internal thermometer is charged under nitrogen with 2,3-dihydro-2-*tert*-butyldimethylsiloxy-1*H*-indene (10.6 g, 42.66 mmol) and 75 mL of dry acetonitrile (Note 1). The flask is immersed in a preheated oil bath and the resulting solution is refluxed such that approximately 25 mL of the solvent is distilled off at atmospheric pressure (Note 9). The solution is allowed to reach ambient temperature and the distillation head is replaced by a glass stopper. Bismuth tribromide (1.32 g, 2.94 mmol) (Notes 1, 10) is added in one portion and stirring is continued for 10 min. The glass stopper is then replaced by a rubber septum. Triethylsilane (8.2 mL, 51.34 mmol) (Note 1) is added via syringe over 5 min causing the immediate formation of a black suspension. The mixture is cooled in an ice-water bath to 0–5 °C before trimethylacetaldehyde (5.1 mL, 46.96 mmol) (Note 1) is added via syringe at such a rate (Note 11) as to maintain the internal temperature below 15 °C. The ice-water bath is removed, the mixture is allowed to warm to ambient temperature over 30 min and stirring is continued for an additional 30 min. (Note 12). The mixture is filtered through a pad of Celite (Note 13) to remove the black precipitate. The filtrate is concentrated by rotary evaporation (40 °C/10 mmHg) to give a mixture of clear and orange oils. To this residue are added 100 mL of *n*-heptane and 40 g of silica gel (Notes 1, 14). The mixture is concentrated by rotary evaporation (40 °C/10 mmHg) to afford a free-flowing powder that is placed at the top of a column (4.5 x 38 cm) of 100 g of silica gel. The column is eluted with *n*-heptane (1 L) followed by 2% ethyl acetate in *n*-heptane (about 1.2 L) to give 7.51 g (86 %) of 2,3-dihydro-2-(2',2'-dimethylethoxy)-1*H*-indene as a colorless oil (Notes 15, 16).

2. Notes

1. Triethylsilane, 2-indanol and trimethylacetaldehyde were purchased from Acros Organics and used as received. Imidazole, *tert*-butyldimethylsilyl chloride and bismuth tribromide were purchased from Aldrich Chemical Company, Inc. and used as received. Dimethylformamide (water content < 0.02%), acetonitrile (water content, 0.003%), ethyl acetate, *n*-heptane and silica gel (200-425 mesh) were purchased from Fisher Scientific and were used as such. The checkers used DMF dried by distillation over CaH₂.

2. The dissolution of 2-indanol and imidazole in dimethylformamide is endothermic. The temperature of the solution changes from 22 °C to 12 °C over 5 min.

3. *tert*-Butyldimethylsilyl chloride was dissolved in DMF by heating the mixture in warm water bath (40 °C).

4. The progress of the reaction is monitored by TLC on silica gel (elution with 10% ethyl acetate in *n*-heptane; visualized with 254-nm UV lamp and phosphomolybdic acid). The product TBS ether has an $R_f = 0.81$ and the alcohol starting material an $R_f = 0.19$. TLC analysis indicates that the reaction is complete after stirring for 45 min at room temperature.

5. The temperature rises from 21 °C to 35 °C upon addition of water.

6. An orange-brown rag layer is formed at the interface of the phases and is removed by filtration through a pad of Celite (3.0 g in 4.5 cm diameter Büchner funnel) to facilitate separation of the layers.

7. The submitters reported a yield of 23.7 g (95%). The spectral data for 2,3-dihydro-2-*tert*-butyldimethylsiloxy-1*H*-indene are as follows: ^1H NMR (400 MHz, CDCl_3) δ : 0.08 (s, 6 H), 0.89 (s, 9 H), 2.87 (dd, $J = 5.9$, 15.6 Hz, 2 H), 3.11 (dd, $J = 6.8$, 15.6 Hz, 2 H), 4.63–4.69 (m, 1 H), 7.11–7.18 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ : –4.7, 18.2, 25.9, 42.6, 73.9, 124.5, 126.4, 141.2. IR (neat): 2952, 2929, 2856, 1471, 1461, 1252, 1101, 1064, 987 cm^{-1} .

8. The product is > 96% pure as determined by GC analysis on a 0.53 mm i.d. x 30 m capillary column (DB-1) at 50–260 °C, heating increment 25 °C/min. Retention time is 7.4 min.

9. Partial distillation azeotropically removes traces of water.

10. Bismuth tribromide is hygroscopic and should be handled in a glove box. Use of wet BiBr_3 in this reaction significantly lowers the yield of the product.

11. The reaction is highly exothermic. However, the exotherm is easily controlled by external cooling and slow (10 min) addition of trimethylacetaldehyde.

12. The reaction is monitored by TLC on silica gel (2% ethyl acetate in *n*-heptane; product $R_f = 0.56$, TBS ether $R_f = 0.39$) and is complete after 30 min at room temperature.

13. Celite (3.0 g) is used on top of a filter paper in a 4.5 cm diameter Büchner funnel.

14. The evaporation of *n*-heptane removes any residual acetonitrile that causes poor separation of the product from the silicon by-products.

15. The spectral data for 2,3-dihydro-2-(2',2'-dimethylethoxy)-1*H*-indene are as follows: ^1H NMR (400 MHz, CDCl_3) δ : 0.90 (s, 9 H), 2.95 (dd, $J = 5.2, 16.0$ Hz, 2 H), 3.13 (s, 2 H), 3.16 (dd, $J = 6.8, 16.0$ Hz, 2 H), 4.26–4.33 (m, 1 H), 7.13–7.16 (m, 2 H), 7.17–7.21 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 26.8, 32.0, 39.4, 79.6, 80.7, 124.6, 126.3, 141.2; IR (neat): 2952, 2866, 1480, 1362, 1110, 1091 cm^{-1} ; Calcd for $\text{C}_{14}\text{H}_{20}\text{O}$: 204.1514; found: 204.1516 ($[\text{M}^+]$).

16. The product is >99% pure as determined by GC analysis performed under the same conditions as described in Note 8. The retention time of the product is 6.7 min.

Safety and Waste Disposal Information

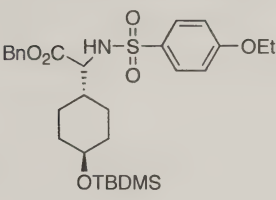

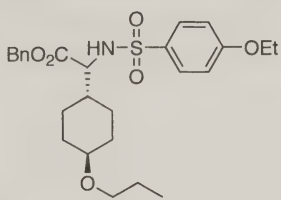
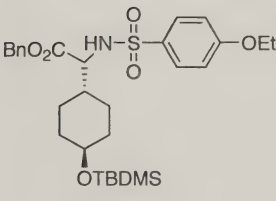

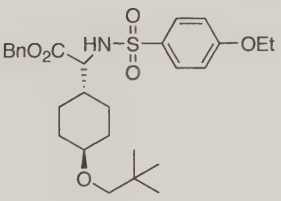
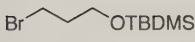
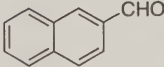
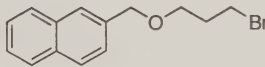
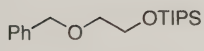

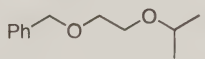


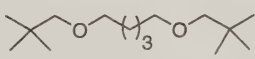
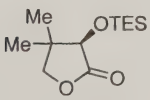

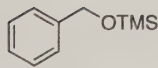

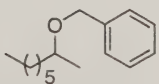
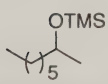
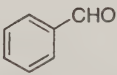
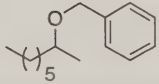
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Ethers are usually prepared by the Williamson method whereby an alkoxy anion is reacted with an alkyl halide or sulfonate.² The presence of base-labile functionalities in the reactants and competing eliminations with the use of secondary and tertiary halides can limit the use of this method. Alternatively, ethers can be synthesized by triethylsilane-mediated reductive alkylation of carbonyl compounds catalyzed by various Lewis acids such as TrClO_4 ,³ BF_3OEt ,⁴ TMSOTf ,⁵ and metal triflates.⁶ As compared to these catalysts, bismuth tribromide was found to work more efficiently.⁷

The present method for the preparation of ethers is a variation of the procedure originally described by Komatsu,⁷ who used only TMS ethers as the substrates. Since TMS ethers are hydrolytically rather labile, the reaction was successfully extended⁸ to more stable silyl ethers such as triethylsilyl (TES), triisopropylsilyl (TIPS) and *tert*-butyldimethylsilyl (TBDMS) ethers (Table 1). The reaction is very sensitive to moisture. Even a trace amount of water in the reaction mixture leads to a substantial amount of desilylated by-product alcohol.⁹ Therefore, it is necessary that the solvent and the reagents are rigorously anhydrous. The reaction is highly exothermic, however, the exotherm is easily controlled by slow addition of aldehyde and by external

Table 1. Transformation of Silyl Ethers into Dialkyl Ethers with BiBr_3 and Et_3SiH

Silyl Ether	Aldehyde or Ketone	Product	Yield (%)
			88 ^a
			92 ^a
			81 ^a
			85 ^a
			45 ^a
		No Reaction	0 ^a
			96 ^b
			88 ^b

^a Reference 8; ^b Reference 7.

cooling. We believe that BiBr₃ by itself does not act as a Lewis acid. Instead, it reacts with Et₃SiH to generate elemental bismuth, hydrogen bromide and triethylsilylbromide.⁸

Overall, the procedure described above constitutes a general and effective method for the synthesis of dialkyl ethers. Its utility and scope are evident from the examples compiled in Table 1, some of which are not easily accessible by the classical Williamson's method.

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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

1*H*-indene, 2-(2,2-dimethylpropoxy)-2,3-dihydro-2-Indanol: 1*H*-Inden-2-ol, 2,3-dihydro-; (4254-29-9)
 Silane, [(2,3-dihydro-1*H*-inden-2-yl)oxy](1,1-dimethylethyl)dimethyl-; (216884-03-6)
 Imidazole: 4*H*-Imidazole; (288-32-4)
tert-Butyldimethylsilyl chloride: Silane, chloro(1,1-dimethylethyl)-dimethyl-; (18162-48-6)

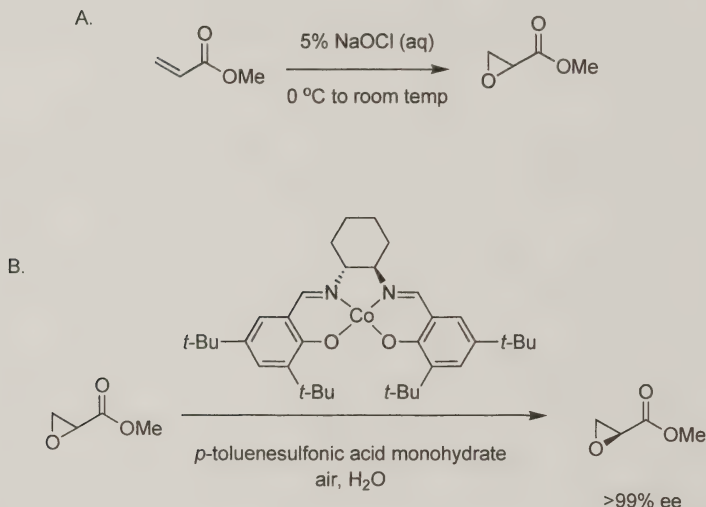
Bismuth bromide: Bismuthine, tribromo-; (7787-58-8)

Triethylsilane: (617-86-7)

Trimethylacetaldehyde: Propanal, 2,2-dimethyl-; (630-19-3)

PREPARATION OF (S)-METHYL GLYCIDATE VIA HYDROLYTIC KINETIC RESOLUTION

(Oxiranecarboxylic acid, methyl ester, (2S)-)



Submitted by Christian P. Stevenson, Lars P. C. Nielsen and Eric N. Jacobsen.¹

Checked by Jason D. McKinley, Timothy D. White, Michel A. Couturier, and John Ragan.

1. Procedure

A. (\pm)-Methyl glycidate (Note 1). A 3-L, round-bottomed flask equipped with a magnetic stir bar and an internal thermometer is charged with aqueous sodium hypochlorite solution (6.0 wt%, 940 mL, 0.755 mol, Note 2) and cooled to 0 °C in an ice bath. Methyl acrylate (58.5 g, 0.680 mol, 1 equiv) is added in one portion, and the flask is capped loosely under air (Note 3). The biphasic mixture is stirred vigorously at 0 °C (Note 4). After 30 min, the ice bath is removed, and the solution is stirred for an additional 1.5 h (Note 5). During this time, the internal temperature gradually rises to 30–37 °C, and the biphasic, yellow mixture becomes turbid and colorless. The reaction mixture is then cooled to 20–25 °C in an ice bath, transferred to a separatory funnel, and extracted with

dichloromethane (4 x 150 mL). The organic extracts are dried over sodium sulfate, filtered, and concentrated to a volume of approximately 50 mL by rotary evaporation (Note 6). The solution is transferred to a 100-mL recovery flask and purified by fractional vacuum distillation (bp 84–87 °C/70 mmHg, Notes 7-9) to afford racemic methyl glycidate (30.3–31.6 g, 44–46%) as a colorless liquid (Note 10).

B. (*S*)-Methyl glycidate. A 200-mL, round-bottomed flask equipped with a magnetic stir bar is charged with (*R,R*)-(-)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (0.916 g, 1.52 mmol, 0.50 mol%), *p*-toluenesulfonic acid monohydrate (0.304 g, 1.60 mmol, 0.53 mol%, Note 11), and dichloromethane (20 mL). The solution rapidly turns from bright red to dark green/brown and is stirred open to air for 30 min (Note 12). After removing the stir bar, the solution is concentrated by rotary evaporation, then the residue is dried under vacuum (<1 mmHg) for 30 min (Note 13). The stir bar is returned to the flask, racemic methyl glycidate (31.0 g, 0.304 mol, 1 equiv) is added, and the flask is loosely capped with a greased glass stopper (Note 14). After dissolving most of the catalyst residue by swirling the solution for 1-2 min, distilled water (3.85 mL, 0.214 mol, 0.70 eq) is added, the reaction vessel is immersed in a room temperature water bath and stirred vigorously for 24 hours. The stopper and water bath are removed, and the reaction flask is fitted with a reflux condenser. The mixture is heated at 85-90 °C (oil bath temperature) for two h. Upon cooling to room temperature and stirring for 30 min, the precipitated red (salen)Co(II) complex is recovered by vacuum filtration, and washed with distilled water (3 x 15 mL, Notes 15 and 16). The filtrate is extracted with dichloromethane (3 x 60 mL). The combined organic extracts are dried over sodium sulfate, filtered, and concentrated to a volume of less than 20 mL by rotary evaporation (Note 6). This brown solution is transferred to a 50-mL recovery flask, and short path vacuum distillation (bp 54–57 °C/33 mmHg, Notes 7-9) affords (*S*)-methyl glycidate (11.1-11.4 g, 36-37%) as a colorless liquid in >99% enantiomeric excess (Notes 10 and 17).

2. Notes

1. This procedure is a modification of that described by Nemes and coworkers,² first developed in these laboratories by K. B. Hansen.³

2. The checkers used 6 wt% NaOCl (Aldrich). The submitters used Clorox® brand household bleach solution (5.25 wt% NaOCl), which required 1.07 L to achieve 0.755 mol.

3. For both procedures, reagents were purchased from Aldrich Chemical Company, Inc. (the submitters purchased (salen)Co(II) pre-catalyst from Strem Chemicals, Inc.). All reagents were used as received without further purification.

4. Rapid stirring must be maintained to ensure sufficient mixing of the biphasic reaction.

5. Longer reaction times lead to diminished yields due to saponification of methyl glycidate under the basic reaction conditions (pH = 11–12).

6. Care should be taken to minimize losses of the volatile methyl glycidate. The submitters concentrated the solution at 20 °C/40 mmHg and lost <2% of the material.

7. Upon reaching 115 mmHg, the pressure of the distillation apparatus is lowered slowly. Vigorous stirring is maintained to keep the solution from foaming over into the receiving flask. Upon reaching the desired distillation pressure, the apparatus is maintained at room temperature with vigorous stirring for one hour to ensure removal of all residual solvent.

8. The receiving flask is maintained at 0 °C once the product starts to distill. At the end of the distillation, when the distillation head temperature starts to fall, the head is warmed gently with a heat gun to maximize product recovery.

9. The submitters reported a boiling point of 59–61 °C/20 mmHg. The checkers found that distillation at slightly higher pressures provided a more distinct boiling point separation between residual solvent/starting material and the product epoxide.

10. The product was found to be >98% pure by gas chromatography on a 30 m HP5 capillary column from Agilent Technologies, Inc. (65 °C isothermal, t_R = 1.31 min). The product has been characterized as follows: ^1H NMR (400 MHz, CDCl_3) δ : 2.92 (dd, J = 6.0, 4.0, 1 H), 2.95 (dd, J = 6.0, 2.5, 1 H), 3.43 (dd, J = 4.0, 2.5, 1 H), 3.77 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 46.5, 47.1, 52.3, 169.9; IR (neat) cm^{-1} : 1740, 1441, 1394, 1298, 1209, 1027, 883; HRMS (m/z) (CI NH_3) calc. for $\text{C}_4\text{H}_{10}\text{NO}_3$ ($\text{M}+\text{NH}_4$) $^+$ 120.0661, found 120.0661; d = 1.16 g/mL. Distilled racemic methyl glycidate stored for two years at 0 °C under air showed no decomposition by ^1H NMR and GC analysis. However, this racemate developed an undetectable contaminant that significantly retarded the rate of the resolution (14 h, 25% ee vs 93% ee with freshly prepared epoxide). Even redistilled, the old epoxide was never as reactive as freshly prepared material. Enantioenriched product isolated from procedure B did not develop this contaminant upon storage.

11. Similar results can also be obtained by replacing *p*-toluenesulfonic acid with electron-deficient benzoic acids, although these catalysts require somewhat higher loadings (for example, 0.7 mol% (salen)Co(II) with 3,5-bis(trifluoromethyl)benzoic acid, 0.8 mol% (salen)Co(II) with 3,5-dinitrobenzoic acid, or 0.9 mol% (salen)Co(II) with 4-nitrobenzoic acid). Such electronic tuning of the catalyst may be beneficial for certain epoxides (see Discussion).

12. Oxidation to the catalytically active Co(III) complex is dependent on maintaining sufficient oxygenation of the solution. Use of a smaller flask or slow stirring can lead to incomplete oxidation and substantially slower kinetic resolution reactions.

13. If desired, this catalyst may be further purified by suspension in pentane, filtration, and drying under vacuum. This provides the (salen)Co(III)OTs·H₂O catalyst as a free-flowing, green powder. This catalyst remains fully active for at least four months when stored under air on the benchtop. Reactions with this catalyst are initiated by simply adding the (salen)Co(III) species to a stirring mixture of epoxide and water at room temperature.^{4d}

14. A glass stopper is preferable to a septum, which can absorb solvent and epoxide.

15. Heating the mixture to reflux induces catalyst reduction and allows removal of most of the Co-containing species by filtration. The aqueous extraction serves to remove most of the diol product. This workup procedure was developed to eliminate catalyst- and diol-induced foaming during distillation of the epoxide. This is not a significant problem in the hydrolytic kinetic resolution of many other epoxides, in which case direct distillation of the epoxide from the reaction mixture remains the most convenient isolation method.⁴

16. After drying under vacuum for 1 h, the recovered (salen)Co(II) complex (0.758-0.789 g, 83-86% recovery) can be recycled without any further purification. The reuse of this catalyst has been demonstrated by resolving an additional 31.0 g of methyl glycidate by using recovered (salen)Co(II) (plus a small amount of fresh complex to reach the desired 0.5 mol% catalyst loading).

17. The enantiomeric purity was determined by chiral gas chromatography on a 20 m Chiraldex γ -TA capillary column from Advanced Separation Technologies, Inc. Using an 80°C isothermal method, the (*R*)- and (*S*)- enantiomers had retention times of 4.1 and 7.3 min, respectively. The optical rotations of (*S*)-methyl glycidate were found to be $[\alpha]_D^{27} -17.3$ (neat) and $[\alpha]_D^{26} -10.3$ (methanol, c 5.34).

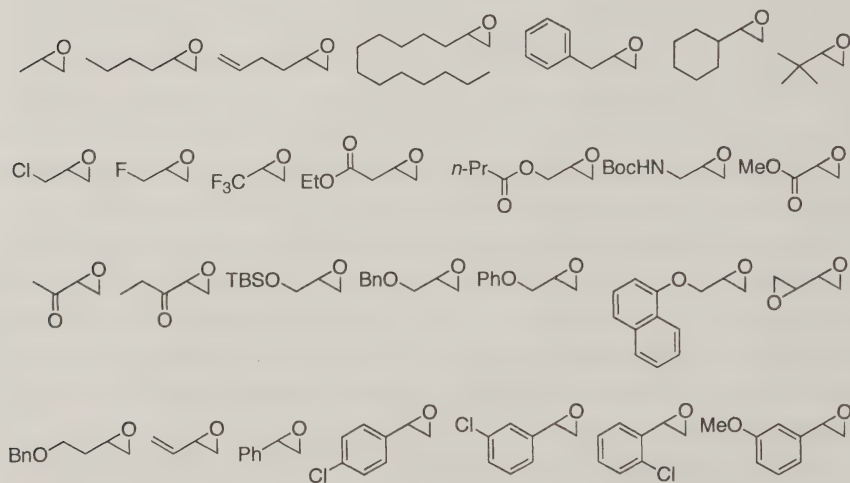
Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by chiral (salen)Co complexes affords highly enantioenriched unreacted epoxides and 1,2-diol products.⁴ The HKR displays extraordinary scope, as a wide assortment of sterically and electronically varied epoxides can be resolved to $\geq 99\%$ ee (Figure 1). The general availability of racemic

Figure 1: Epoxides Resolved to $>99\%$ ee via the HKR^{4c}

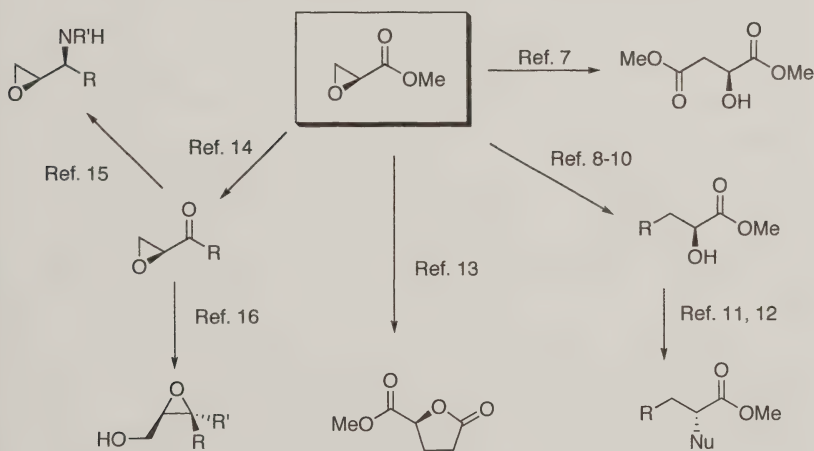


epoxides, the use of water as the resolving agent, and the low loadings of a recyclable, commercially available catalyst make this methodology particularly practical. Accordingly, the utility of the HKR has already been widely demonstrated in organic synthesis.⁵ Recent mechanistic studies^{4d} have revealed that the more electrophilic (salen)Co(III)OTs catalyst is significantly more reactive than the (salen)Co(III)OAc catalyst originally reported.^{4a-c} The increased Lewis acidity of the (salen)Co(III)OTs catalyst has, however, been shown to be detrimental to the HKR's of styrene oxide

and propargyl epoxides, presumably due to participation of less selective S_N1 pathways.

While the broad utility of epoxides as synthetic intermediates has been well documented,⁶ methyl glycidate is a particularly versatile chiral building block. A range of reactions has been developed that selectively transform either the epoxide or ester functionality (Scheme 1). The epoxide can be converted to an α -hydroxyester by carbonylation⁷ or by organocuprate,⁸ phenol,⁹ or indole¹⁰ addition. The resulting hydroxyl group can then be displaced under Mitsunobu conditions¹¹ or as the sulfonate.¹² The epoxide can also be opened with 1-morpholino-2-trimethylsilyl acetylene yielding a γ -lactone.¹³ Alternatively, methyl glycidate can be converted to a variety of epoxyketones by addition of Grignard or organolithium reagents.¹⁴ The resulting epoxyketones undergo diastereoselective reductive amination,¹⁵ or can be converted to tri-substituted epoxyalcohols by using a Grignard addition/Payne rearrangement protocol.¹⁶

Scheme 1: Synthetic Uses of Methyl Glycidate



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16. Luchi, J. T.; Jacobsen, E. N., Unpublished results.

Appendix
Chemical Abstract Nomenclature;
(Registry Number)

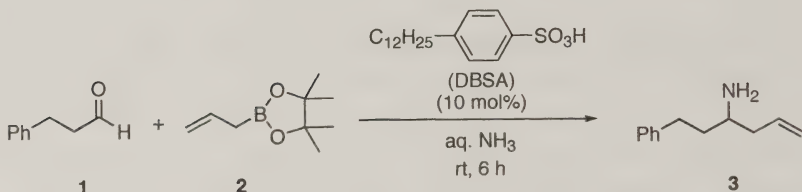
(*S*)-Methyl glycidate: Oxiranecarboxylic acid, methyl ester, (*2S*)-; (118712-39-3)

Methyl acrylate: 2-Propenoic acid, methyl ester; (96-33-3)

(±)-Methyl glycidate: Oxiranecarboxylic acid, methyl ester; (4538-50-5)

(*R,R*)-(-)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II): Cobalt, [[2,2'-[(1*R*,2*R*)-1,2-cyclohexanediylbis[(nitrilo-κ*N*)methylidyne]]bis[4,6-bis(1,1-dimethylethyl)phenolato-κ*O*]](2-)]-, (SP-4-2)-; (176763-62-5)

ALLYLBORONATION OF IMINES: 1-PHENYLHEX-5-EN-3-AMINE



Submitted by Masaharu Sugiura, Keiichi Hirano, and Shu Kobayashi.¹

Checked by Nai-Wen Tseng and Mark Lautens.

1. Procedure

Caution! The reaction should be conducted in a well-ventilated hood.

An oven-dried, 250-mL, two-necked, round-bottomed flask is charged with dodecylbenzenesulfonic acid (1.307 g, 4.0 mmol) (Note 1), flushed with argon, and equipped with a magnetic stirring bar, a rubber septum, and an argon inlet. The flask is charged with 80 mL of 28% aqueous ammonia (Note 2) by syringe. After the gas evolution ceases, the mixture is stirred at 23–25 °C to give a clear solution, then cooled to 0 °C in an ice-water bath. 2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2) (8.120 g, 9.0 mL, 48.3 mmol) (Note 3) is added dropwise over 5 min via a syringe (Note 4) and the mixture is stirred at 23–25 °C for 30 min. 3-Phenylpropionaldehyde (1) (5.328 g, 5.3 mL, 39.7 mmol) (Note 5) is added dropwise via a syringe over 5 min at 23–25 °C. The slurry mixture is vigorously stirred at 23–25 °C for 6 h (Note 6) and transferred to a 1-L separatory funnel with water (100 mL) and saturated aqueous NaCl solution (200 mL). The aqueous layer is extracted three times with diethyl ether (200, 150, and 150 mL), and the combined organic layers are washed with saturated aqueous NaCl solution (200 mL), dried over anhydrous sodium carbonate (Na₂CO₃), filtered, and concentrated under reduced pressure to afford crude amine 3 as a yellow oil (Note 8). The crude material is chromatographed on a 5.5 x 45 cm column containing 300 g of silica gel (Note 9). A mixture of hexane/isopropyl amine (20/1) is used as the eluent. Fractions (27 mL each) are collected in 30-mL test tubes (Note 10). Fractions containing the product are evaporated under

reduced pressure (30 °C, 200 mmHg) to afford the amine as yellow oil. In order to completely remove the pinacol, the amine is diluted with diethyl ether (200 mL) and extracted three times with 1 M hydrochloric acid (3 x 50 mL). The combined aqueous layers are washed twice with diethyl ether (2 x 100 mL), carefully basified with 6 M sodium hydroxide (60 mL) (Note 7), and extracted three times with dichloromethane (200, 150, and 150 mL). The combined organic layers are dried over anhydrous sodium carbonate (Na_2CO_3), filtered, concentrated under reduced pressure (30 °C, 200 mmHg) and dried under vacuum (approximately 0.2 mmHg, 15 min) to afford 6.680 g of **3** (96%) as yellow oil (Note 11).

2. Notes

1. Dodecylbenzenesulfonic acid (soft type) (>90.0%) was purchased from Tokyo Kasei Kogyo Co., Ltd. or TCI America, and used without purification. This viscous liquid material was measured directly in the reaction flask using a 5-mL pipette.

2. Aqueous ammonia solution (25.0-27.9%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received. The checkers used aqueous ammonia solution (28.0-30.0%) purchased from Aldrich Chemical Company, Inc.

3. 2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2**) (95%) was purchased from Aldrich Chemical Company, Inc. This material included white precipitates. Therefore, it was filtered with diethyl ether, evaporated (30 °C, 200 mmHg), and distilled (72-73 °C, 27 mmHg, the boiling point is uncorrected) prior to use.

4. On addition of **2**, colorless precipitates were formed to give a slurry mixture.

5. 3-Phenylpropionaldehyde (**1**) (>90% GC) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used after distillation. The checkers purchased this reagent from Aldrich Chemical Company, Inc.

6. As the reaction progressed, the precipitates gradually dissolved to give a cloudy solution. The reaction could be monitored by TLC analysis on Merck silica gel 60 F₂₅₄ plates and visualization with UV and phosphomolybdic acid [sodium phosphomolybdate hydrate (9.7 g) in 85% phosphoric acid (6.0 mL), concentrated sulfuric acid (20 mL), and water

(400 mL)]. The checkers used 5% phosphomolybdic acid in ethanol as the TLC indicator. Disappearance of **1** was observed within 30 min. Compound **1** has $R_f = 0.68$ with hexane/ethyl acetate (3/1) as eluent (UV absorption, gray spot). Compound **3** has $R_f = 0.13$ with hexane/ethyl acetate (1/1) as eluent and $R_f = 0.63$ with hexane/isopropyl amine (10/1) as eluent (UV absorption, white spot). Pinacol has $R_f = 0.30$ with hexane/ethyl acetate (1/1) as eluent and $R_f = 0.33$ with hexane/isopropyl amine (10/1) as eluent (UV inactive, blue spot).

7. After addition of sodium hydroxide, the pH was checked by a pH-test paper to be approximately 9.

8. The crude material was a mixture of **3** and pinacol (ca. 10/1 molar ratio). Distillation under reduced pressure (88 °C, 3 mmHg) gave almost pure **3**, but could not separate pinacol completely.

9. Silica gel 60 70-230 mesh ASTM (Merck Ltd.) was used. Checkers used Silica gel 60 40-63 mm (EMD Chemicals, Inc.).

10. The column fractions were checked by TLC analysis on Merck silica gel 60 F₂₅₄ plates with hexane/isopropyl amine (20/1) as eluent and visualization with UV and phosphomolybdic acid. R_f values are given in Note 6.

11. The physical properties of **3** are as follows: ¹H NMR (300 MHz, CDCl₃) δ: 1.26 (brs, 2 H), 1.61 (dddd, $J = 13.6, 10.1, 7.9, 5.7$ Hz, 1 H), 1.76 (dddd, $J = 13.5, 10.3, 6.2, 5.4$ Hz, 1 H), 2.03 (dddt, $J = 13.8, 7.9, 7.9, 0.9$ Hz, 1 H), 2.27 (dddt, $J = 13.7, 6.3, 4.8, 1.4$ Hz, 1 H), 2.64 (ddd, $J = 13.6, 10.1, 6.2$ Hz, 1 H), 2.75 (ddd, $J = 13.7, 10.2, 5.7$ Hz, 1 H), 2.82 (tt, $J = 7.9, 4.6$ Hz, 1 H), 5.09 (dm, $J = 10.0$ Hz, 1 H), 5.10 (dm, $J = 17.2$ Hz, 1H), 5.79 (dddd, $J = 17.2, 10.0, 7.9, 6.4$ Hz, 1 H), 7.15–7.21 (m, 3 H), 7.25–7.30 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ: 32.6, 39.4, 42.7, 50.1, 117.4, 125.7, 128.31, 128.33, 135.6, 142.2; HR-ESIMS calcd for C₁₂H₁₈N (M+H⁺) 176.1439, found 176.1435; Anal. Calcd for C₁₂H₁₇N: C, 82.23; H, 9.78; N, 7.99. Found: C, 81.92; H, 9.77; N, 7.89.

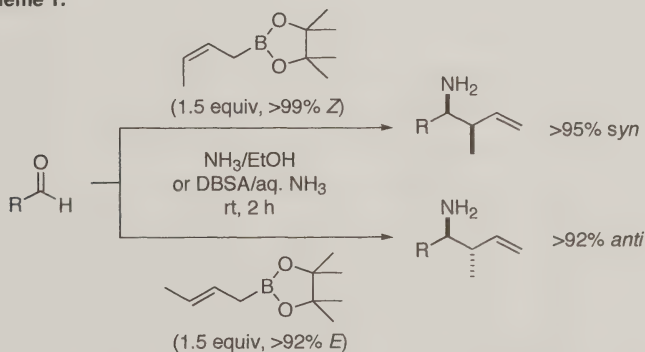
Safety and Waste Disposal Information

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3. Discussion

Addition of allylmetals to C=N double bonds is a useful synthetic method for formation of homoallylic amine derivatives.² However, in order to obtain synthetically versatile homoallylic primary amines, removal of substituents on the nitrogen is often necessary. To address this issue, hydrolytically labile *N*-silyl, *N*-boryl, or *N*-metalloimines have been utilized frequently as precursors to the primary amines; however, pre-formation of those imines are required. In contrast, the method in this procedure is based on in situ formation of ammonia-derived imines and subsequent chemoselective allylation.^{4,5} Thus, homoallylic primary amines are directly obtained from the three components without incorporation and cleavage of *N*-substituents. Additionally, when (*E*)- and (*Z*)-crotylboronates are used, *anti*- and *syn*-crotylated products can be obtained with high diastereoselectivities, respectively (Scheme 1).

Scheme 1.

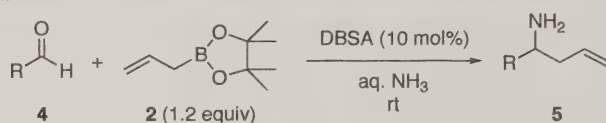


$R = Ph, p\text{-NO}_2C_6H_4, CO_2H, 2\text{-pyridyl etc.}$

Use of ammonia as the nitrogen source is key in this process. In contrast to ammonia, primary amines scarcely undergo the reaction, and hence highly selective formation of homoallylic primary amines (suppression of over-reaction of the products) has been attained. Although ammonia in ethanol was utilized previously,⁴ use of aqueous ammonia in the presence of DBSA has made the reaction more practical.⁵ A variety of additives were examined for the reaction of 3-phenylpropionaldehyde (**1**) with allylboronate (**2**) in aqueous ammonia. Among them, DBSA was

found to be the best, whereas lauric acid, sodium dodecyl sulfate, and sodium dodecylbenzenesulfonate were effective as well. In the absence of any additive, the yield of **3** and the chemoselectivity of the reaction (formation of **3** vs the corresponding homoallylic alcohol) were low. The hydrophobic alkyl chain of DBSA plays an important role, since *p*-toluenesulfonic acid showed much lower activity. In reactions performed with DBSA, a variety of aliphatic, aromatic, heteroaromatic, and α,β -unsaturated aldehydes afford the corresponding homoallylic primary amines in good to excellent yields (Table 1).⁵

Table 1.

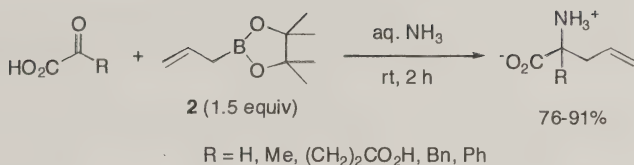


entry	R (4)	time/h	%yield of 5 ^a
1	Ph	6	61
2	<i>p</i> -NO ₂ C ₆ H ₄	6	60
3	<i>p</i> -MeOC ₆ H ₄	6	60
4	<i>o</i> -HOC ₆ H ₄	6	75
5	2-Pyridyl	6	88
6	3-Pyridyl	2	85
7	4-Pyridyl	2	83
8	2-Thienyl	6	60
9	3-Thienyl	2	95
10	2-Furyl	2	53
11	3-Furyl	2	93
12	(<i>E</i>)-PhCH=CH	2	78
13	<i>c</i> -C ₆ H ₁₁	6	68
14	<i>n</i> -C ₅ H ₁₁	2	49

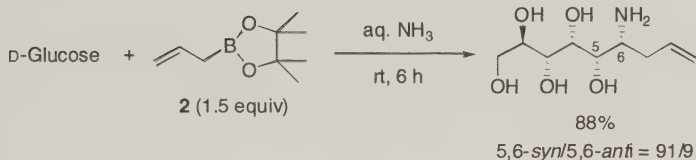
^a Isolated yields.

However, addition of DBSA is not always necessary; hydrophilic carbonyl compounds such as α -oxo carboxylic acids and hydroxy aldehydes or ketones, including carbohydrates, were found to undergo the reactions smoothly with high selectivity as shown in Schemes 2 and 3.⁶

Scheme 2.



Scheme 3.



1. Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
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6. Unpublished results.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Dodecylbenzenesulfonic acid; (27176-87-0)

2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: 1,3,2-Dioxaborolane,
4,4,5,5-tetramethyl-2-(2-propenyl)-; (72824-04-5)

3-Phenylpropionaldehyde: Benzenepropanal; (104-53-0)

TRIFLUOROMETHYLATION AT THE α -POSITION OF
 α,β -UNSATURATED KETONES:
4-PHENYL-3-(TRIFLUOROMETHYL)BUTAN-2-ONE



Kazuyuki Sato,¹ Masaaki Omote, Akira Ando, Itsumaro Kumadaki.*
Checked by Scott E. Denmark and Won-jin Chung.

1. Procedure

4-Phenyl-3-trifluoromethyl-2-butanone. A flame-dried, 500-mL, four-necked, round-bottomed flask is equipped with a rubber septum, a dry ice/isopropyl alcohol cooled cold-finger condenser topped with a nitrogen stopcock inlet, a pressure-equalizing dropping funnel topped with a rubber septum, a Teflon-coated thermocouple (Note 1), and a Teflon-coated magnetic stirring bar. The reaction vessel is charged with 4-phenylbut-3-en-2-one (7.310 g, 50 mmol), RhCl(PPh₃)₃ (925 mg, 1.0 mmol) (Note 2), and 190 mL of tetrahydrofuran (THF) is added under nitrogen (Note 2). The brown solution is cooled in an isopropyl alcohol bath to $-30\text{ }^{\circ}\text{C}$ (Note 3). In a graduated tube equipped with a three-way stopcock attached to a nitrogen inlet from a Schlenk line, 7 mL (ca. 86 mmol) of trifluoroiodomethane (CF₃I) (Note 4) is condensed at $-78\text{ }^{\circ}\text{C}$ by using a dry ice/isopropyl alcohol bath. After the CF₃I condenses, the three-way stopcock is closed and the top of the stopcock is fitted with a rubber septum. The condensed CF₃I is added to the reaction mixture quickly through a cannula by warming the graduated tube with a water bath. After almost all of CF₃I is transferred to the reaction vessel, 10 mL of THF is added to the graduated test-tube through the septum, and the THF is transferred to the reaction vessel through the cannula by briefly evacuating the reaction vessel through a hose to the Schlenk line. The reaction mixture is immersed in an ice-bath, and then diethylzinc in hexane solution (75 mL 1.0 M) (Note 5) is gradually added to the solution through the pressure-equalizing dropping funnel over 2 h. During the addition, the temperature of the solution is kept below $5\text{ }^{\circ}\text{C}$ by cooling with an ice bath. The reaction mixture is allowed to warm to room temperature over 30 min after removing the ice-bath, whereupon it is stirred at room temperature for 1

h (Note 6). The progress of the reaction is followed by thin layer chromatographic (TLC) analysis (Note 7), which confirms that the reaction is complete (Note 8). The resulting mixture is carefully poured into a mixture of 10% HCl (150 mL) and ice (about 50 g) in a 1-L Erlenmeyer flask equipped with a Teflon-coated magnetic stirring bar (Note 9). The ice melts in a few minutes, then the mixture is extracted with Et₂O (4 x 150 mL). The combined organic layers are washed with brine (100 mL) and then are dried over MgSO₄ (about 20 g). The MgSO₄ is removed by filtration through a sintered glass-filter, and the solvent is removed under reduced pressure on a rotary evaporator (23 °C, 30 mm Hg). The residue is purified by silica gel (Note 10) column chromatography (190 g, diameter = 50 mm, eluted with hexane/ethyl acetate, 30/1; 1.2 L) to remove small amounts of impurities and most of the black color. The product-containing portions are concentrated under reduced pressure, and are purified by reduced-pressure distillation using short path distillation apparatus (66–68 °C / 3 mmHg) to afford 7.610 g (72 %) of 4-phenyl-3-(trifluoromethyl)butan-2-one as a clear, colorless oil (Notes 10 and 11).

2. Notes

1. A PFA coated thermocouple probe, Type K (Omega Engineering, Inc.) was inserted through the septum.

2. 4-Phenylbut-3-en-2-one (>99%) and RhCl(PPh₃)₃ (>99.99%) were purchased from Aldrich Chemical Co. and were used without further purification. The reaction apparatus is shown in Figure 1. The submitters used argon.

3. Anhydrous THF was obtained by filtration through an alumina drying column on a GlassContour system (Irvine, CA).

4. CF₃I was purchased from Aldrich Chemical Co. (99%). Its boiling point is –22.1 °C, and density is about 2.4 g/mL. CF₃I was transferred from the container to the graduated test-tube by using the apparatus shown in Figure 2. The tube was evacuated and cooled below –78 °C in a dry ice/isopropyl alcohol bath. Then the vacuum line was closed, stopcock A was opened and the correct amount of CF₃I was collected in the graduated test-tube.

5. Diethylzinc (1.0 M in hexane solution) was purchased from Aldrich Chemical Co. It was transferred to the pressure-equalizing addition funnel via cannula by briefly evacuating the reaction flask through the Schlenk line.

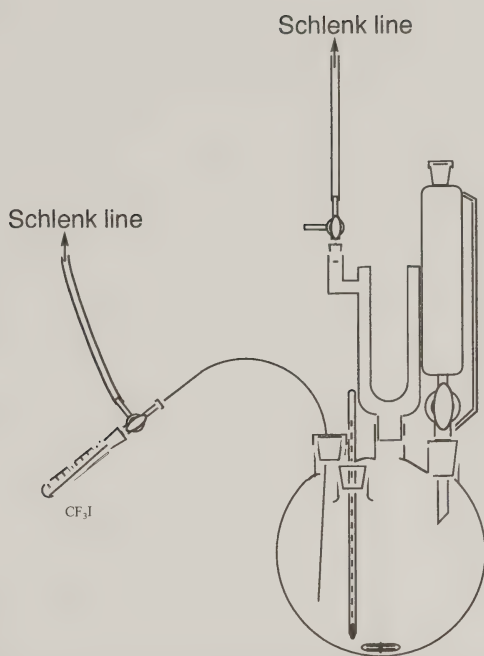


Figure 1. Reaction Apparatus for the Synthesis of α - CF_3 Ketones

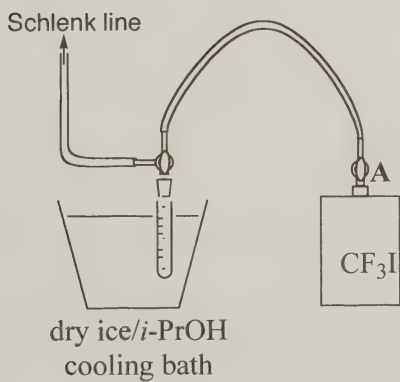


Figure 2. Apparatus for Collecting CF_3I

6. A mild evolution of gas was observed upon addition of diethylzinc. The composition of the gas was not determined, but it is most likely trifluoromethyl iodide and/or ethylene. As the reaction mixture was warmed to room temperature, slight gas evolution was observed, and the color of the solution changed to dark brown.

7. TLC analysis was performed on Merck silica gel plates with QF-254 indicator and hexane/ethyl acetate, 9/1 as eluent. Visualization was accomplished with UV light and KMnO_4 staining solution.

8. An aliquot of the reaction mixture was removed and quenched with 10% aq. HCl, then Et_2O was added. The organic phase was analyzed by TLC (see Note 7). 4-Phenylbut-3-en-2-one ($R_f = 0.23$) almost disappeared after 0.5 h, but 4-phenylbutan-2-one, ($R_f = 0.29$) which can be generated by quenching the corresponding rhodium enolate was still present. After 1.0 h, 4-phenylbutan-2-one disappeared and only 4-phenyl-3-(trifluoromethyl)butan-2-one ($R_f = 0.50$) was detected. The submitters used gas chromatography to monitor the reaction progress.

9. Vigorous evolution of gas was observed upon quenching.

10. The submitters found that 4-phenyl-3-(trifluoromethyl)butan-2-one is stable at room temperature under an argon atmosphere over three months.

11. The final product had the following characteristics; ^1H NMR (CDCl_3 , 500 MHz) δ : 2.08 (s, 3 H), 3.06 (dd, 1 H, $J = 13.8, 4.3$ Hz), 3.18 (dd, 1 H, $J = 13.8, 10.8$ Hz), 3.56 (dq, 1 H, $J = 10.8, 8.6, 4.1$ Hz), 7.15–7.32 (m, 5 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ : 31.6 (q, $J_{\text{C-F}} = 1.8$ Hz), 31.8 (q, $J_{\text{C-F}} = 2.8$ Hz), 57.4 (q, $J_{\text{C-F}} = 24.9$ Hz), 124.4 (q, $J_{\text{C-F}} = 279.5$ Hz), 127.0, 128.7, 128.8, 136.4, 201.3 (q, $J_{\text{C-F}} = 1.5$ Hz); ^{19}F NMR (CDCl_3 , 396 MHz) δ : –67.72 (d, 3 F, $J = 7.5$ Hz); IR (KBr) cm^{-1} : 3033, 2942, 1731, 1606, 1499, 1457, 1422, 1362, 1301, 1263, 1161, 1115, 1081, 1505, 874, 747, 704; MS m/z : 216 (M^+); HRMS Calc. $\text{C}_{11}\text{H}_{11}\text{OF}_3$: 216.0762 (M^+), Found: 216.0763; Elemental Analysis Calc. for $\text{C}_{11}\text{H}_{11}\text{OF}_3$: C, 61.11; H, 5.13; F, 26.36. Found: C, 60.87; H, 5.04; F, 26.68.

Safety and Waste Disposal Information

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3. Discussion

Trifluoromethylated (CF_3) compounds constitute one of the most important classes of fluorine-containing compounds, and there are many reports on trifluoromethylation reactions. However, the reactions for introducing a CF_3 group at the α -position of ketones are limited to trifluoromethylation of metal enolates of carbonyl compounds or imides,² electrophilic trifluoromethylation with calcogenium reagents,³ and photochemical^{4a} and ultrasonic^{4b} reactions of enamines with CF_3I .

Recently, our group reported that α,β -unsaturated ketones react with ethyl bromodifluoroacetate and Et_2Zn in the presence of a rhodium catalyst to give unexpected products, in which either the CF_2COOEt group was introduced on the α -carbon of α,β -unsaturated ketones or the expected 1,2-addition product proceeded in good yields depending on the solvent.⁵ On the basis of this result, we treated α,β -unsaturated ketones with CF_3I in the presence of Et_2Zn and $\text{RhCl}(\text{PPh}_3)_3$ to prepare $\alpha\text{-CF}_3$ ketones.⁶ This method was found to be superior to previous routes for synthesis of $\alpha\text{-CF}_3$ ketones because it did not need special reagents, could be carried out under mild conditions, and provided the product in good yield. Moreover, trifluoromethylation at the α -position of α,β -unsaturated ketones had not been reported.

A mechanistic proposal is shown below (Figure 3).⁶ A β -hydrogen atom in Et_2Zn appears to play an important role in this reaction because dimethylzinc does not work at all.

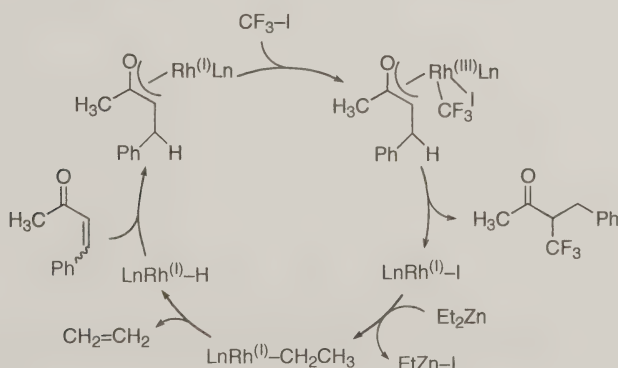


Figure 3. Proposed Mechanism

Following the procedure described above, various α -CF₃ ketones were obtained in good yields as shown in Table 1. The yields reported in the Table are based on reactions performed on a 2-mmol scale.

Table 1. Synthesis of Various α -CF₃ Ketones

$\text{CF}_3\text{I} + \text{R}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{R}' \xrightarrow[\text{THF}]{\text{Et}_2\text{Zn}, \text{RhCl}(\text{PPh}_3)_3} \text{R}-\text{C}(=\text{O})-\text{C}(\text{CF}_3)(\text{H})-\text{CH}_2-\text{R}'$			
entry	enone	time (h)	yield (%) ^(a)
1		0.5	77
2		1	31
3		1	35
4		3	0
5		1	67
6		1	59
7		1	65
8		1	65
9		0.5	55
10		1	53
11		0.5	0 ^(b)

(a) Isolated yield. (b) 1,4-adduct was obtained in 54%.

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Appendix

Chemical Abstracts Nomenclature (Registry Number)

4-Phenyl-3-buten-2-one; (122-57-6)

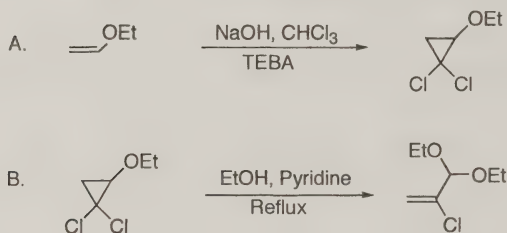
RhCl(PPh₃)₃: Rhodium, chlorotris(triphenylphosphine)-, (SP-4-2)-;
(14694-95-2)

Trifluoroiodomethane; (2314-97-8)

Diethylzinc; (557-20-0)

4-Phenyl-3-(trifluoromethyl)butan-2-one: 2-Butanone, 4,4,4-trifluoro-3-(phenylmethyl)-; (808105-43-3)

SYNTHESIS OF 2-CHLOROACROLEIN DIETHYL ACETAL (2-Chloroprop-2-enal, diethyl acetal)



Submitted by Ole H. Kvernenes and Leiv K. Sydnes.¹

Checked by David M. Arnold and Peter Wipf.²

1. Procedure

A. 1,1-Dichloro-2-ethoxycyclopropane. A 250-mL, three-necked, round-bottomed flask equipped with a septum, a 3.8 cm Teflon-coated magnetic stir bar and a condenser connected to a drying tube containing Drierite[®] is charged with ethyl vinyl ether (9.55 mL, 7.20 g, 0.10 mol) (Note 1), chloroform (31.9 mL, 47.8 g, 0.40 mol) (Note 2), and benzyltriethylammonium chloride (TEBA) (0.100 g, 0.44 mmol) (Note 3) and placed in an ice bath (Note 4). After the reaction flask is cooled for 10 min, the mixture is stirred vigorously (Note 5) and 24 g of a 50% aqueous solution of sodium hydroxide (NaOH) (12.0 g, 0.30 mol in 12 mL of H₂O) (Note 6) is added dropwise via a syringe in 10 min (Note 7). The reaction mixture is stirred vigorously at bath temperature (approximately 0 °C) for 2 h and at room temperature for 22 h. The reaction mixture is then cooled in an ice bath and quenched by injecting 6 M hydrochloric acid (30 mL) dropwise over a 10 min period (Note 8). The hydrolysate is transferred to a 500-mL separatory funnel, and the flask is rinsed with water (2 x 20 mL) and dichloromethane (30 mL), which is also added to the funnel. After addition of more water (60 mL) to the funnel, the mixture is shaken and the organic layer is separated from the aqueous layer. The aqueous layer is extracted with dichloromethane (3 x 60 mL) (Note 9). The combined organic extracts are dried with approximately 2 g of anhydrous magnesium sulfate (MgSO₄) (Note 10), vacuum filtered, and concentrated under reduced pressure on a rotary evaporator (25 °C at 70 mmHg) to afford a pale yellow

residue. This residue is transferred to a 50-mL round bottom flask using approximately 2 mL of dichloromethane (Note 11). The dichloromethane is removed at 30–35 °C (oil bath temperature) at 50 mmHg, and the product is distilled at 65–70 °C (oil bath temperature) at 30 mmHg to give 12.94 g (84%) (Note 12) of 1,1-dichloro-2-ethoxycyclopropane (Note 13) as a colorless liquid, bp 55 °C/30 mmHg.

B. 2-Chloro-3,3-diethoxyprop-1-ene (Note 14). A 250-mL, single-necked, round-bottomed flask equipped with a 3.8 cm Teflon-coated magnetic stir bar and a condenser connected to a Drierite® drying tube is charged with absolute ethanol (50 mL) (Note 15), pyridine (7.33 mL, 7.20 g, 0.09 mol) (Note 16) and 1,1-dichloro-2-ethoxycyclopropane (10.86 g, 0.070 mol) (Note 17). The resulting mixture is stirred at a moderate speed at reflux for 48 h in an oil bath at 95 °C (bath temperature), and is then allowed to cool to room temperature before being concentrated under reduced pressure on a rotary evaporator (40 °C at 70 mmHg vacuum) until the volume is approximately 20 mL (Note 18). The residue is transferred to a 250-mL separatory funnel, and the flask is rinsed with water (2 x 50 mL) and dichloromethane (60 mL), which are also added to the separatory funnel. The mixture is shaken, and the organic layer is separated from the aqueous layer. The aqueous phase is extracted with dichloromethane (2 x 50 mL), and the combined organic phases are washed with a 0.7 M aqueous solution (2 x 100 mL) of copper sulfate (CuSO₄) (Note 19), and dried with approximately 2 g of anhydrous magnesium sulfate (Note 10). The organic phase is then vacuum filtered into a 500-mL round-bottomed flask through a plug of aluminum oxide (Note 20). Dichloromethane (15 mL) is added to the flask containing the MgSO₄ and after mixing the contents for approximately 1 min, the dichloromethane solution is filtered through the plug as well. The combined filtrates are then concentrated under reduced pressure on a rotary evaporator (25 °C at 70 mmHg) and transferred with approximately 2 mL of dichloromethane to a 50-mL round-bottomed flask for vacuum distillation (Notes 11, 21). The dichloromethane is removed at 21 °C and 30 mmHg. Following the removal of the dichloromethane, the apparatus is placed again under vacuum (30 mmHg) and the 25-mL receiving flask is submerged in an acetone/dry ice bath. The product is distilled with an oil bath temperature of 80–85 °C. Upon completion of the distillation, nitrogen gas is bled into the apparatus from the vacuum adaptor as the vacuum is released. The receiving flask is warmed to room temperature under a nitrogen atmosphere before being removed. The distillation yields 6.75 g (59 %) of a clear liquid, bp 70–71 °C/30 mmHg

(Note 22). The product, 2-chloro-3,3-diethoxyprop-1-ene (Note 23), is found by GC analysis to be 96.0–97.2% pure (Notes 24, 25, 26).

2. Notes

1. Ethyl vinyl ether of 99% purity was purchased from Aldrich Chemical Co. and used as obtained.

2. Chloroform, with a purity of better than 99%, was purchased from J. T. Baker (Mallinckrodt Baker) and used as obtained.

3. Checkers used TEBA, a phase-transfer catalyst, which was 98% pure, purchased from Acros Organics, and used as obtained. Submitters used 99% pure TEBA purchased from Aldrich Chemical Co.

4. The bath was a Pyrex dish (125 mm x 65 mm), to which were added about 300 mL of ice and 300 mL of cold water.

5. It is essential that the stirring is vigorous so that the organic and aqueous phases are thoroughly mixed. The submitters used a mechanical stirrer with a stirring speed of approximately 500 revolutions per min.

6. Sodium hydroxide, with a purity of 98.4%, was purchased from J. T. Baker and used as obtained. A 50% stock solution of sodium hydroxide was made by dissolving 20.0 g of sodium hydroxide in 20.0 g of water.

7. The submitters report that the sodium hydroxide solution can be added much faster without any consequences at the scale used here. At larger scales, however, it is important to add the solution slowly to avoid excessive heating. When the reaction was carried out on a 2-mole scale, the addition of 240 g of 50% aqueous sodium hydroxide required 30 min.

8. The hydrochloric acid was prepared by dilution of concentrated (36–38%, 1.19 g/mL, 12 M) hydrochloric acid of Baker-analyzed quality purchased from J. T. Baker (Mallinckrodt Baker). Rapid addition of the hydrochloric acid solution at room temperature generated a lot of heat and discoloration (yellowing) of the reaction mixture was noted.

9. Dichloromethane with a purity of 99.5% was purchased from EMD Chemicals Inc. and used as obtained.

10. Checkers used anhydrous magnesium sulfate that was purchased from EMD Chemicals Inc. and used as obtained. Submitters used dehydrated but not completely anhydrous magnesium sulfate from several suppliers.

11. Checkers carried out the distillation with a 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a short path distillation head fitted with a 25-mL receiving flask. Submitters used standard equipment consisting of a 100-mL pear-shaped flask with a

magnetic stirrer, a connecting adapter with thermometer, a Liebig condenser, a vacuum adapter, and a 25-mL receiving flask, all with 14/23 joint(s).

12. The reaction was also run at a 50% scale and yielded 5.64 g of product. The yield range is 73–84%. The submitters report that the reaction has been reproduced up to a 2-mole scale following the procedure described here. At such a large scale, the yield is considerably better, usually in the 82–96% range, provided proper care is taken to avoid excessive heating of the reaction mixture (see Notes 7 and 8). When the reaction is carried out on a larger scale, the amount of product remaining in the distillation flask, the distillation head and the condenser is relatively smaller.

13. The product exhibits the following spectroscopic properties: ^1H NMR (CDCl_3 , 300 MHz) δ : 1.29 (t, 3 H, $J = 7.0$ Hz), 1.53 (dd, 1 H, $J = 8.5$, 5.1 Hz), 1.66 (t, 1 H, $J = 8.5$ Hz), 3.54 (dd, 1 H, $J = 8.1$, 5.1 Hz), 3.68–3.89 (m, 2 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 14.9, 27.9, 58.6, 63.1, 67.3; IR (neat) 3095 (w), 2980 (s), 2931 (m), 2875 (m), 1481 (w), 1444 (w), 1425 (m), 1398 (m), 1374 (m), 1345 (m), 1300 (w), 1235 (m), 1179 (m), 1115 (m), 1065 (s), 1019 (m), 977 (w), 905 (m), 890 (w), 800 (m), 766 (s) cm^{-1} ; EI-MS m/z 158 ($[\text{M}+4]^+$, 0.1), 156 ($[\text{M}+2]^+$, 0.5), 154 (M^+ , 0.8), 119 (54), 109 (17), 97 (34), 91 (100), 84 (9), 73 (8), 61 (62), 55 (8). The purity of the product was >99% based on GC analysis (assuming identical response factors) using a HP 6890 Series GC system (100% dimethylpolysiloxane coated column (30 m x 320 μm x 0.25 μm); column flow rate 1 mL/min; 70 $^\circ\text{C}$ - start; temperature increased at 15 $^\circ\text{C}/\text{min}$ until 240 $^\circ\text{C}$; temperature kept at 240 $^\circ\text{C}$ for 5 min; temperature increased at 25 $^\circ\text{C}/\text{min}$ until 300 $^\circ\text{C}$; retention time: 3.975 min.

14. The procedure for this step is a modification of that described by Skattebøl.³

15. Checkers used absolute ethanol containing at least 99.95% ethanol without further purification as purchased from Pharmco Products Inc. Submitters used at least 99.98% pure absolute ethanol without further purification as purchased from Arcus, Norway.

16. Anhydrous pyridine, with a purity of 99.8%, was purchased from Aldrich Chemical Co. and was used without further purification. Submitters report that at least 1 equiv of pyridine has to be used; usually 1.3 equiv are used. If less than 1 equiv is used, ethanol addition to the product takes place, furnishing 2-chloro-1,1,3-triethoxypropane.

17. The order of addition does not affect the reaction yield.

18. When the volume is approximately 20 mL, the liquid turns turbid upon cooling. A slight yellowing of the solution was noted.

19. Checkers used copper sulfate pentahydrate, with a purity of >99%, purchased from Fisher Scientific to prepare the aqueous copper sulfate solution by dissolving 35.0 g of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in 200 mL of water. Submitters used copper sulfate pentahydrate, with a purity of 98 %, purchased from Acros Organics.

20. Checkers used activated basic aluminum oxide (150 mesh, 58 Å) purchased from Aldrich Chemical Co. Submitters used the Fluka Chromatography product 6300, neutral 120–125 mesh aluminum oxide. The filtration was carried out using a column with a diameter of 2.0 cm and a height of 10 cm containing a vacuum adaptor connected to a water aspirator; upon addition of 6.3 g of aluminum oxide the alumina plug was 2.0 cm high.

21. Distillation of the product has to be carried out with care to avoid loss of material due to the high volatility of this alkene.

22. The reaction was also reproduced on a 50% scale and yielded 2.86 g of product for a yield range of 50-59%.

23. The product exhibits the following spectroscopic properties: ^1H NMR (CDCl_3 , 300 MHz) δ : 1.23 (t, 6 H, $J = 7.0$ Hz), 3.47–3.68 (m, 4 H), 4.84 (s, 1 H), 5.45 (dd, 1 H, $J = 1.2, 0.5$ Hz), 5.66 (t, 1 H, $J = 1.2$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 15.1, 61.8, 100.7, 115.1, 138.2; IR (neat) 2978 (s), 2886 (s), 1635 (m), 1481 (w), 1445 (m), 1372 (m), 1336 (m), 1296 (w), 1206 (m), 1062 (s), 964 (m), 904 (m), 765 (w), 747 (w) 703 (w), 677 (w) cm^{-1} ; EI-MS m/z 166 ($[\text{M}+2]^+$, 4), 164 (M^+ , 13), 129 (10), 119 (84), 103 (60), 91 (100), 75 (14), 63 (9), 55 (8); HRMS m/z calculated for $\text{C}_7\text{H}_{13}\text{O}_2\text{Cl}$ 164.0604, found 164.0612. Analysis calcd. for $\text{C}_7\text{H}_{13}\text{O}_2\text{Cl}$: C, 51.07; H, 7.96; found C, 50.90; H, 7.88.

24. The purity of the product was 96.0–97.2% according to GC analyses. The GC analyses (assuming identical response factors) were performed with a HP 6890 Series GC system (100% dimethylpolysiloxane column (30 m x 320 μm x 0.25 μm); column flow rate 1 mL/min; 70 $^\circ\text{C}$ - start; temperature increased at 15 $^\circ\text{C}/\text{min}$ until 240 $^\circ\text{C}$; temperature kept at 240 $^\circ\text{C}$ for 5 min; temperature increased at 25 $^\circ\text{C}/\text{min}$ until 300 $^\circ\text{C}$; retention time: 4.410 min.

25. ^1H NMR and GC analyses determined that the product was contaminated with 2.8–4.0% of 1,1-dichloro-2-ethoxycyclopropane. Subsequent distillations did not improve the purity of the product above 97.2%.

26. An aliquot of the product mixture was resubjected to the reaction conditions, heated at reflux for an additional 24 h and worked up according to the outlined procedure. A GC analysis performed under identical conditions as above showed this product to be >99% pure.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

2-Haloacrolein diethyl acetals are densely functionalized compounds with a considerable potential in organic synthesis. This potential has been partly realized with 2-bromoacrolein diethyl acetal, which has proven to be useful for attachment of the 1-(diethoxymethyl)ethenyl group to a variety of substrates in multistep syntheses.⁴⁻¹⁵ The chloro analogue, however, has barely been used,¹⁶ probably due to its tedious synthesis.

Both 2-chloroacrolein diethyl acetal and 2-bromoacrolein diethyl acetal can be prepared from acrolein,^{9,17,18} but the syntheses are hampered by the ease of polymerization of this unsaturated aldehyde.¹⁹ Thus, the starting material should be thoroughly purified to facilitate product formation,²⁰ and an elaborate work-up procedure must be applied to obtain a pure product.⁹ Furthermore, it is a disadvantage that hazardous chlorine gas and bromine liquid are used as reagents.

An alternative synthesis of 2-chloroacrolein diethyl acetal, involving ring opening of 1,1-dichloro-2-ethoxycyclopropane, has been reported by Skattebøl.³ The cyclopropane is prepared from ethyl vinyl ether following the Doering-Hoffman procedure (CHCl_3 , *t*-BuOK, pentane, low temperature), which is rather laborious and requires absolutely dry conditions.²¹ An alternative synthesis of the cyclopropane, using CCl_4 , CH_2Br_2 , 50% aqueous NaOH, and tetrabutylammonium hydrogensulfate, has also been published,²² but the method is rather unattractive due to the use of toxic CCl_4 .²³ A third procedure involves vinyl ether, chloroform and magnesium,²⁴ but this synthesis is conceivably difficult to run on a large scale.

Inspired by Skattebøl's synthesis, we have worked out a new and simpler procedure for the preparation of the title compound. 1,1-Dichloro-2-ethoxycyclopropane is synthesized from ethyl vinyl ether by using Makosza's method with chloroform instead of CCl_4 .²⁵ This method has been used to prepare other 2-alkoxy-1,1-dichlorocyclopropanes,²⁵⁻²⁷ albeit in lower yields than obtained in this case. The purification of the cyclopropane

is straightforward, and it is rewarding that the yield is improved when the reaction is preformed on larger scales.²⁸ The ring opening of the cyclopropane has also been modified compared to Skattebøl's method. Pyridine, added to remove the hydrogen chloride formed during the ring opening, is removed effectively by washing with a solution of copper(II) sulfate, which forms water-soluble complexes with pyridine.²⁹ Subsequent filtration through an aluminum-oxide pad was also introduced to remove any pyridine-copper complex remaining in the combined organic phases.

The yield of 2-chloroacrolein diethyl acetal in the second step is lower than what has been reported in the literature.³ This is probably because we have performed the distillation in such a way that contamination of the corresponding acetylenic acetal, 1,1-diethoxy-2-propyne, was avoided.

1. Department of Chemistry, University of Bergen, Allégt. 41, NO-5007 Bergen, Norway.
2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Ethyl vinyl ether: Ethene, ethoxy-; (109-92-2)

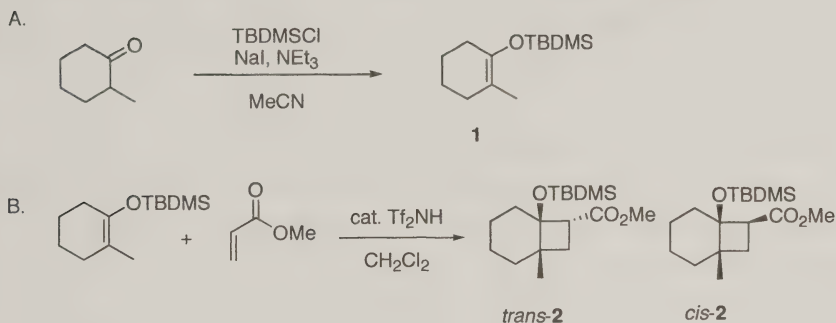
Benzyltriethylammonium chloride; Benzenemethanaminium, *N,N,N*-triethyl-, chloride; (56-37-1)

1,1-Dichloro-2-ethoxycyclopropane; cyclopropane, 1,1-dichloro-2-ethoxy-; (7363-99-7)

Copper sulfate pentahydrate; Sulfuric acid copper(2+) salt (1:1), pentahydrate; (7758-99-8)

**TRIFLUOROMETHANESULFONIMIDE-CATALYZED
(2 + 2)-CYCLOADDITION OF SILYL ENOL ETHERS
WITH α,β -UNSATURATED ESTERS:**

1-(*tert*-BUTYLDIMETHYLSILOXY)-8-(METHOXYCARBONYL)-6-METHYLBICYCLO[4.2.0]OCTANE



Submitted by Kiyosei Takasu, Takayuki Ishii, Kazato Inanaga and Masataka Ihara.¹

Checked by Katarzyna Kowalczyk and John A. Ragan.

1. Procedure

A. *1-tert-Butyldimethylsilyloxy-2-methyl-1-cyclohexene*. A nitrogen-purged, 300-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a glass stopper, a temperature probe, and a nitrogen inlet adapter. The flask is charged with 2-methylcyclohexanone (10.0 mL, 82.6 mmol) (Note 1), triethylamine (13.9 mL, 100 mmol) (Note 2), and *t*-butyldimethylsilyl chloride (TBDMSCl) (15.1 g, 100 mmol) (Note 1). To the flask is added a solution of sodium iodide (15.0 g, 100 mmol) (Note 1) in acetonitrile (100 mL) (Note 3) via syringe over 30 min at ambient temperature. The reaction solution is stirred at ambient temperature for 18 h. The resulting mixture is quenched by addition of saturated sodium bicarbonate solution (100 mL). The mixture is extracted with hexane twice (2 x 200 mL). The combined organic phases are washed with brine (40 mL) and dried over MgSO₄, filtered and concentrated at reduced pressure (15–25 mmHg, 25–35 °C) to afford crude product **1**

(20.2 g) as a pale yellow oil. This crude product is purified by filtration through a silica gel pad (200 g of silica in a 10-cm diameter fritted glass funnel, height of silica was 20 cm), rinsing with 1 L of hexanes (Note 4) to provide 17.75–17.80 g (95%) of **1** as a colorless oil (Notes 5, 6).

B. *1-(tert-Butyldimethylsilyloxy)-8-(methoxycarbonyl)-6-methylbicyclo[4.2.0]octane*. A flame-dried, 300-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, an internal temperature probe and an argon inlet adapter. The flask is charged with a solution of **1** (4.98 g, 22.0 mmol) in dichloromethane (100 mL) (CH_2Cl_2) (Note 7) at ambient temperature, and the mixture is cooled in a dry ice-acetone bath to $-78\text{ }^\circ\text{C}$ while methyl acrylate (1.80 mL, 20.0 mmol) (Note 8) is added. To the mixture is added dropwise a solution of trifluoromethanesulfonimide (80 mM solution; 2.50 mL, 0.20 mmol) in toluene (Notes 9, 10) via syringe over 30 min at $-78\text{ }^\circ\text{C}$ (Note 11). The mixture is stirred at $-78\text{ }^\circ\text{C}$ for 30 min (Note 12), and is then quenched with saturated sodium bicarbonate solution (100 mL). The mixture is extracted with methyl *tert*-butyl ether (MTBE) (2 x 100 mL) (Note 13). The combined organic phases are dried over MgSO_4 , filtered and concentrated at reduced pressure (15–25 mmHg, 25–35 $^\circ\text{C}$) to afford crude product **2** (7.80 g) as a colorless oil. This crude product is purified by chromatography with 400 g of silica gel (6.5 cm i.d. column, eluent with 50:1 hexane/ Et_2O) (Note 14) to provide 5.13–5.27 g (82–84%) of the *trans*-diastereomer of **2** as a colorless oil (Notes 15, 16).

2. Notes

1. 2-Methylcyclohexanone (>98%), *t*-butyldimethylsilyl chloride (97%), and sodium iodide (>99.5%) were purchased from Aldrich Chemical Company and used as received.

2. Triethylamine (anhydrous) was purchased from J. T. Baker and used as received.

3. Acetonitrile (anhydrous, Sure-Seal) was purchased from Aldrich Chemical Company and used as received.

4. The checkers used 40- μm silica gel for the filtration (J. T. Baker). The submitters purified the product by column chromatography (9.5 cm i.d. column, elution with hexane) on 400 g of Silica gel 60 N (spherical, neutral,

63–210 mesh), purchased from Kanto Chemical Co. Inc. The R_f value for **1** is 0.75 (hexane).

5. The product from step A exhibits the following data: IR (neat): 2928, 2857, 1687, 1348, 1253, 1168, 831 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 0.10 (s, 6 H) 0.94 (s, 9 H), 1.51–1.55 (m, 2 H), 1.56 (s, 3 H), 1.60–1.66 (m, 2 H), 1.92–1.95 (m, 2 H), 1.98–2.02 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ : –3.6, 16.6, 18.4, 23.2, 24.1, 26.1, 30.5, 30.6, 111.7, 143.2; MS (EI) m/z : 226 (50%), 169 (80%), 75 (100%); Anal. Calcd for $\text{C}_{13}\text{H}_{26}\text{OSi}$: C, 68.96; H 11.57. Found: C, 68.64; H, 11.64.

6. A trace amount (<3%) of the regioisomeric silyl enol ether (1-*tert*-butyldimethylsiloxy-6-methyl-1-cyclohexene) was observed by ^1H NMR spectroscopy. Separation of the isomer is not required for the next reaction.

7. Dichloromethane (anhydrous, Sure-Seal) was purchased from Aldrich Chemical Company and used as received.

8. Methyl acrylate (97%) was purchased from Aldrich Chemical Company and used as received. The submitters purchased this material from Tokyo Kasei Kogyo Co., Ltd., and distilled under reduced pressure before use.

9. Trifluoromethanesulfonimide (95%) was purchased from Aldrich Chemical Company, Inc. A 80 mM solution of trifluoromethanesulfonimide in toluene was prepared as follows. A flame-dried, 50-mL, round-bottomed flask equipped with gas inlet is charged with trifluoromethanesulfonimide (675 mg, 2.40 mmol) under an atmosphere of argon, and toluene (anhydrous, Aldrich Sure-Seal) (30 mL) is quickly added under an atmosphere of argon. The solution can be stored for more than 1 month in the dark at ambient temperature.

10. Trifluoromethanesulfonimide (neat) is moisture-sensitive and, if possible, should be dissolved in toluene under an argon atmosphere after a fresh bottle is opened.

11. The solution temperature inside the reaction vessel was monitored by the internal thermometer and kept within –76 to –78 $^{\circ}\text{C}$.

12. Since the (2 + 2)-cycloaddition reaction is reversible, the effects of temperature, reaction time, concentration, and solvent are important. The *trans*-isomer of **2** corresponds to the kinetic product. Interestingly, on

smaller scale reactions (~100 mg of silyl enol ether), the submitters obtained *trans*- and *cis*-isomers of **2** in 98% and 1% yields, respectively, under the same conditions.

13. The submitters performed these extractions with diethyl ether. The checkers found that MTBE worked equally well for this extraction.

14. Chromatography was performed on 40- μ m silica gel purchased from J. T. Baker. The R_f values for *trans*- and *cis*-isomers of **2** are 0.26 and 0.22, respectively (50:1; hexane/Et₂O), as reported by the submitters. The checkers were unable to cleanly discern the minor isomer on TLC.

15. The *trans*-isomer exhibits the following spectroscopic properties: IR (neat) ν : 2929, 2857, 1734, 1462, 1220, 1095, 834 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ : 0.05 (s, 3 H), 0.10 (s, 3 H), 0.84 (s, 9 H), 1.03 (s, 3 H), 1.14–1.60 (m, 8 H), 1.62–1.64 (m, 1 H), 1.78 (t, J = 10, 1 H), 3.10 (t, J = 10, 1 H), 3.62 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ : –3.2, –2.9, 18.6, 20.3, 21.8, 24.9, 26.0, 26.9, 32.3, 33.4, 41.3, 48.5, 51.1, 77.6, 173.6; LRMS (EI) m/z : 255 (M^+ – 57, 100%); Anal. Calcd for C₁₇H₃₂O₃Si: C, 65.33; H 10.32. Found: C, 65.22; H, 10.78.

16. The checkers were unable to isolate a clean sample of the minor isomer, although its presence was confirmed in the crude ¹H NMR spectrum (approximately a 10:1 ratio of major/minor isomers, which is in agreement with the submitter's report). The submitters reported the isolation of the *cis*-isomer of **2** (8%), which exhibited the following characterization data: IR (neat): 1746 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ : 0.05 (s, 3 H), 0.09 (s, 3 H), 0.85 (s, 9 H), 0.97 (s, 3 H), 1.08–1.24 (m, 1 H), 1.31–1.61 (m, 5 H), 1.75 (m, 2 H), 2.03 (d, J = 12.2 Hz, 1 H), 2.22 (t, J = 10.0 Hz, 1 H), 3.16 (t, J = 7.8 Hz, 1 H), 3.62 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ : –1.64, –1.58, 18.6, 21.0, 21.6, 24.0, 26.1, 33.4, 33.7, 38.8, 41.0, 43.1, 51.1, 83.7, 172.6; LRMS (EI) m/z : 255 (M^+ – 57); Anal. Calcd for C₁₇H₃₂O₃Si: C, 65.33; H 9.98. Found: C, 65.36; H, 9.98.

Safety and Waste Disposal Information

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3. Discussion

The procedure described here is typical for the catalytic (2 + 2)-cycloaddition reaction of silyl enol ethers with α,β -unsaturated esters to produce multi-substituted silyloxycyclobutanes.² Silyl enol ethers are readily available by enol silylation of the corresponding ketones. Previously, we have reported that the (2 + 2)-cycloaddition of silyl enol ethers is catalyzed by a hard Lewis acid such as EtAlCl_2 .^{3,4,5} Compared with that method, the procedure using trifluoromethanesulfonimide (Tf_2NH) provides high chemical yield and stereoselectivity under practical and environmentally benign conditions, with broader substrate-applicability (Table).

We have found the Tf_2NH -catalyzed (2 + 2)-cycloadditions of silyl enol ethers with α,β -unsaturated esters are eventually reversible. Although the kinetic product in the reaction possesses the *trans*-configuration of silyloxy and ester functionalities, longer reaction times or higher reaction temperatures allow the retro (2 + 2)-cycloaddition to occur, leading to the thermodynamically more stable *cis*-isomer. The isomerization can be monitored by careful TLC analysis.

Yamamoto and coworkers reported that Tf_2NH -catalyzed aldol reactions between TMS enol ethers and aldehydes are promoted by highly reactive, *in situ* generated TMSNTf_2 .⁶ We also observed that a catalytic amount of pre-assembled TBSNTf_2 promoted the (2 + 2)-cycloaddition reactions. Thus, Tf_2NH appears to act similarly as a pre-catalyst to produce the real catalyst TBSNTf_2 through reaction with the *t*-butyldimethylsilyl enol ethers. Importantly, decomposition of TBSNTf_2 to form Tf_2NH during the course of these processes is reversed by reaction of the latter with the TBS enol ether substrates. As a result, high turnover numbers are achieved in this catalytic system. Thus, a reaction using a stoichiometric amount of Tf_2NH results in low yields of the desired product and decomposition of the silyl enol ether.

Table 1. Catalytic (2 + 2)-Cycloaddition Reactions^a

entry	silyl enol ether	α,β -unsaturated esters	products		% yield ^a (ratio)
			<i>trans</i>	<i>cis</i>	
1 ^b					(n = 0) 77 (>99 : 1)
2 ^b					(n = 1) 70 (80 : 20)
3 ^b					(n = 2) 91 (93 : 7)
4 ^b					75 (72 : 28)
5 ^b					93 (81 : 19)
6 ^c					75 (67 : 33)
7 ^c					71 (87 : 13)
8 ^d					(n = 0, R = H) 66 (-)
9 ^d					(n = 1, R = Me) 53 (-)
10 ^d					(n = 2, R = H) 80 (-)
11 ^e					78 (80 : 20) ^h
12 ^f					43 (80 : 20) ^h

^a Reactions are performed using the α,β -unsaturated ester (1 equiv), silyl enol ethers (1.1 equiv) and catalytic amounts of TiF_2NH in CH_2Cl_2 (0.1–0.3 M). ^b TiF_2NH (1.0 mol%), -78°C , 2 h. ^c TiF_2NH (1.0 mol%), -20°C to -40°C , 3 h. ^d TiF_2NH (2.0 mol%), rt, 0.5 h. ^e α,β -unsaturated esters (1.5 equiv), silyl enol ethers (1 equiv), TiF_2NH (1 mol%), -40°C , 0.5 h. ^f α,β -unsaturated ester (2.0 equiv), silyl enol ethers (1 equiv), TiF_2NH (1.0 mol%), -40°C , 3 h. ^g Chemical yields were calculated based on α,β -unsaturated esters except for entries 11 and 12. ^h Chemical yields were calculated based on silyl enol ethers.

1. Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan.
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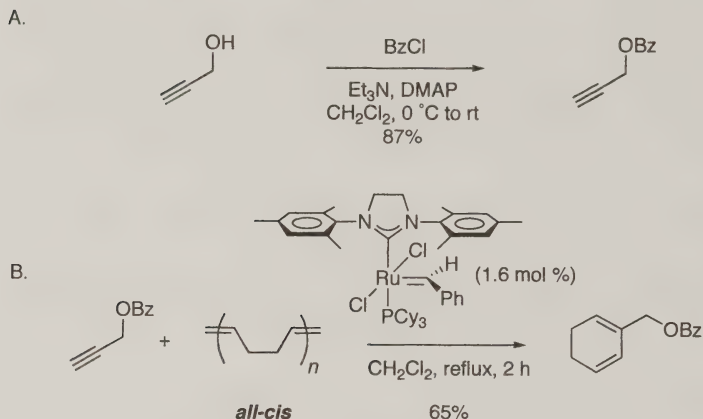
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 1-*tert*-Butyldimethylsilyloxy-2-methyl-1-cyclohexene: Silane,
(1,1-dimethyl- ethyl)dimethyl[(2-methyl-1-cyclohexen-1-yl)oxy]-;
(20152-33-4)
- 1-(*tert*-Butyldimethylsilyloxy)-8-(methoxycarbonyl)-6-methylbicyclo
[4.2.0]octane: Bicyclo[4.2.0]octane-7-carboxylic acid,
6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-methyl-, methyl ester,
(1*R*,6*R*,7*S*)-rel-: (657428-75-6)
- Trifluoromethanesulfonimide: Methanesulfonamide, 1,1,1-trifluoro-*N*-
phenyl-*N*-[(trifluoromethyl)sulfonyl]-; (37595-74-7)
- Methyl acrylate: 2-Propenoic acid, methyl ester: (96-33-3)

2-SUBSTITUTED-1,3-CYCLOHEXADIENES BY INTERMOLECULAR, METHYLENE-FREE TANDEM ENYNE METATHESIS

[2-(Benzoyloxymethyl)-1,3-cyclohexadiene]



Submitted by Amol A. Kulkarni and Steven T. Diver.¹

Checked by Masakatsu Shibasaki and Keisuke Maki.

1. Procedure

A. Propargyl benzoate. Into an oven-dried, argon-cooled 1-L round-bottomed flask equipped with magnetic stirbar and rubber septum is added CH_2Cl_2 (250 mL) (Note 1), which is maintained under an atmosphere of argon (Note 2). Propargyl alcohol (13.6 mL, 240 mmol, 1.2 equiv) and triethylamine (Note 3) (42 mL, 300 mmol, 1.5 equiv) are added by gas-tight syringe, followed by the addition of DMAP (Note 4) (2.4 g, 20 mmol, 0.1 equiv). The reaction mixture is subsequently cooled in an ice bath for 30 min. Benzoyl chloride (Note 5) (23.2 mL, 200 mmol, 1.0 equiv) is then added slowly by syringe over 15 min. The reaction mixture is stirred in the ice bath for an additional 30 min and then warmed to room temperature and stirred for 4 h. The reaction is quenched by addition of ice cold water (300 mL). The contents are transferred into a 1-L separatory funnel. The organic layer is washed with 1 M HCl (2 x 300 mL), followed by distilled water (300 mL) and brine (300 mL). The organic layer is separated, dried (Na_2SO_4) and concentrated under vacuum (rotary evaporator, 8–9 mmHg, 24 °C) (Note 6). The crude yellow oil is purified by bulb-to-bulb distillation (80

°C pot temperature) under reduced pressure (1–2 mmHg) to yield the desired ester (28.4–28.9 g, 89–90% yield) as a colorless oil (Note 7).

B. 2-(Benzoyloxymethyl)-1,3-cyclohexadiene. Into an oven-dried, argon-cooled 100-mL Schlenk tube (Note 8) equipped with a magnetic stirbar, rubber septum and a cold finger condenser (Note 9) under an atmosphere of argon (Note 2) is added all-*cis* polybutadiene (8.66 g, 160 mmol, 8 equiv) (Note 10) followed by 40 mL CH₂Cl₂ (Note 1). To the Schlenk tube is added Grubbs second generation catalyst (Note 11) (271 mg, 0.32 mmol, 1.6 mol %) and the flask is then immersed in an oil bath maintained at 45 °C. Propargyl benzoate (3.2 g, 20 mmole) is dissolved in about 1 mL of CH₂Cl₂ and this solution is added to the suspension of polybutadiene in CH₂Cl₂ over a period of 2 h by means of syringe pump addition with a gas-tight syringe connected to a short section of teflon tubing (Note 12). The reaction flask is maintained at 45 °C during the addition. After the addition is complete, the syringe is rinsed with about 1 mL of CH₂Cl₂ and the contents are added to the reaction mixture over about 10 min. The reaction mixture is stirred at 45 °C for another 30 min. At this stage, ethyl vinyl ether (Note 13) (612 µL, 0.64 mmol, 2 equiv based on ruthenium catalyst) is added and heating is continued for an additional 30 min. The reaction mixture is concentrated under vacuum (rotary evaporator, 8–9 mmHg, 23–25 °C) to give a brown oil which is then partially purified by passing through a plug of silica gel (50 g; 2 x 10 cm) (Note 14) eluting with 0.8 % ethyl acetate in hexanes. The first 250 mL of the eluent is discarded (Note 15). Then 700 mL of 4% ethyl acetate in hexanes is used to elute the desired cyclohexadiene along with other oligomeric materials. The eluent is concentrated under vacuum (rotary evaporator, 10 mmHg, 25–40 °C). The viscous yellow oil thus obtained is further purified by means of bulb-to-bulb distillation (checker; 120–130 °C pot temperature/submitter; 124–128 °C) at reduced pressure (1–2 mmHg) to afford the desired cyclohexadiene derivative as a colorless oil (2.64–2.69 g, 62–63 % yield) (Notes 16,17,18). The ¹H and ¹³C NMR spectra of the isolated compound match previously reported characterization data.²

2. Notes

1. The submitters used argon-sparged dichloromethane (CH₂Cl₂, Mallinckrodt, 99%) drawn from a solvent purifier (two 0.05 m x 1 m stainless steel columns packed with activated alumina) maintained under argon immediately prior to use. The checkers used anhydrous

dichloromethane, which was used as received from Kanto Chemical Co. No degassing of the solvent was performed.

2. Argon was supplied statically through a gas manifold with a mineral oil bubbler to generate slight back-pressure.

3. The submitters used triethylamine (Acros, 99%) distilled from CaH_2 . The checkers used triethylamine (Aldrich, 99.5%) as received.

4. DMAP (99%) was used as received from Aldrich Chemical Co.

5. The submitters used benzoyl chloride (Baker, 99.8%) as received. The checkers used benzoyl chloride (Aldrich, 99%) as received.

6. The submitters used a diaphragm-type vacuum pump equipped with a primary dry ice-acetone cooled condensor (V-shaped cold finger-type) and a secondary in-line vacuum trap (dry ice-acetone cooling) to collect solvent. The checkers used a diaphragm-type vacuum pump equipped with $-20\text{ }^\circ\text{C}$ cooling circulator.

7. Further purification was not necessary; material obtained by bulb-to-bulb distillation was 99.5% pure (GC), and was used in the subsequent step. GC retention time of 11.90 min (capillary GC, HP-5 column, $0.25\text{ }\mu\text{m} \times 30\text{ m}$; temperature program: $40\text{ }^\circ\text{C}$ for 4 min, then increased $25\text{ }^\circ\text{C}/\text{min}$ to $280\text{ }^\circ\text{C}$. To obtain an accurate boiling point, the ester was distilled at $80\text{--}81\text{ }^\circ\text{C}$ (1.1 mmHg) through a short path column. Analytical data is reported for the distillate obtained from the bulb-to-bulb distillation: Analytical TLC: R_f 0.36 (10 % ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ : 2.53 (t, $J = 2.4\text{ Hz}$, 1 H), 4.92 (d, $J = 2.4\text{ Hz}$, 2 H), 7.46 (t, $J = 7.9\text{ Hz}$, 2 H), 7.55 (tt, $J = 7.4, 1.2\text{ Hz}$, 1 H), 8.06-8.08 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 52.4, 75.0, 77.7, 128.4, 129.3, 129.7, 133.3, 165.7; FT-IR (thin film, cm^{-1}) 3296, 1725, 1268, 1108; HRMS (FAB; $\text{M}^+ + \text{H}$, m/z) calcd for $\text{C}_{10}\text{H}_9\text{O}_2$ 161.0602, found 161.0604.

8. The Schlenk tube dimensions were $3.7\text{ cm} \times 18\text{ cm}$ with a sidearm of 9 mm OD. The septum was fitted over the 9 mm tube with argon supplied through an 18-gauge needle. The teflon cannula is threaded through the same septum. Use of a round-bottomed flask in place of the Schlenk tube resulted in incomplete conversion.

9. The submitters reported the use of a cold-finger condenser in the Schlenk tube. The checkers used a standard reflux condenser and obtained identical results.

10. All-*cis* polybutadiene (M_w ca. $2\text{--}3 \times 10^6$, 98% *cis*) was purchased from Aldrich (18137-4) and used without further purification. The polymer was kept in a polyethylene bag and no special precautions were taken to exclude air. The use of fewer equivalents of polybutadiene led to incomplete

conversions. For example, 4.0 equiv of polybutadiene delivered under the same reaction conditions described in this procedure produced only 64% yield of cyclohexadiene (NMR yield against mesitylene internal standard).

11. Ruthenium [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro(phenylmethylene)(tricyclohexylphosphine) (Grubbs second generation catalyst) was obtained from Aldrich Chemical Co. (Milwaukee, WI) or from Materia, Inc. (Pasadena, CA).

12. A Teflon cannula was used (ID = 0.8 mm and 0.4 mm thickness of about 20 cm length). One end of the cannula was attached to the needle by slipping over the 22 gauge stainless steel needle until snug; the other end was cut with a razor blade at a 45° angle and pierced through the rubber septum. The tip of the cannula was touched to the cooled glass surface just below the level of solvent reflux.

13. Ethyl vinyl ether (99%) was used as received from Aldrich Chemical Co.

14. The filtration was carried out using Merck silica gel 60 (230–400 mesh). The viscous crude mixture required high pressure to elute the solvent. The use of a smaller column (<2 cm) was not suitable.

15. This fraction contains oligomeric byproducts including isomeric 1,5,9-cyclododecatrienes. This fraction should be checked for cyclohexadiene product by TLC analysis (R_f 0.42; 10% ethyl acetate in hexanes) before discarding.

16. The submitters reported obtaining a pale yellow oil. The cyclohexadiene is not stable as the neat liquid, even when stored at –20 °C. Partial decomposition by polymerization was variable, and depended significantly on sample storage conditions. When BHT (5 % by weight) was added to the distillate, polymerization was retarded somewhat. Extended storage of the neat cyclohexadiene is not recommended. Pure cyclohexadiene could be obtained from degraded samples by redistillation with loss of material.

17. Further purification was not necessary. In order to obtain an accurate boiling point, the dienylester was distilled at 124–125 °C (1.1 mmHg) through a short path column.

18. The analytical data are provided for the distillate from the bulb-to-bulb distillation: Analytical TLC: R_f 0.42 (10 % ethyl acetate in hexanes). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 2.15–2.26 (m, 4 H), 4.80 (m, 2 H), 5.87–5.93 (m, 2 H), 5.99 (ddd, J = 9.5, 3.4, 1.5 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.55 (tt, J = 7.4, 1.2 Hz, 1 H), 8.05–8.08 (m, 2 H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 22.0, 22.1, 67.0, 124.3, 124.9, 127.6, 128.3, 129.6, 130.3, 131.1,

132.9, 166.5; FT-IR (thin film, cm^{-1}) 2935, 1719, 1450, 1271, 1111, 712; HRMS (FAB; M^+ , m/z) calcd for $\text{C}_{14}\text{H}_{15}\text{O}_2$ 215.1072, found 215.1069. GC was used to assess purity of the cyclohexadiene, which was found to be >98.5%. GC retention time of 15.07 min (capillary GC, HP-5 column, 0.25 μm x 30 m; temperature program 40 $^{\circ}\text{C}$ for 5 minutes, then increased 25 $^{\circ}\text{C}/\text{min}$ to 280 $^{\circ}\text{C}$).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

In recent years, alkene metathesis has emerged as a powerful method for the synthesis of the carbon-carbon double bond. Synthetic applications increased dramatically with the advent of the functional group tolerant ruthenium carbenes developed by Grubbs.³⁻¹¹ Enyne metathesis is a closely related catalytic reaction which involves the coupling of an alkene with an alkyne to give a conjugated 1,3-diene.¹² This is a particularly attractive reaction because the conjugated diene product participates in a host of transformations and can thus be used as a building block for the synthesis of more complex organic molecules.

Recent metathesis applications involving tandem transformations are exciting due to their potential to build rings from simple acyclic precursors. These applications are very attractive because they permit the rapid assembly of complex structures. Tandem metathesis transformations had previously been limited to intramolecular reactions.^{13,14} Though attractive, these tandem reactions require the synthesis of polyenynes reactants. Ring synthesis from unsaturated reactants by an *intermolecular* reaction is advantageous because the reactants are comparatively simple. The difficulty in intermolecular ring building reactions is the initial, non-stereoselective metathesis between the alkene and alkyne component. Control of alkene geometry is a current, general problem in intermolecular metathesis research. The tandem diene-alkyne metathesis described in this procedure is challenging because it is triggered by an intermolecular bond formation which lacks stereocontrol.

The challenge posed by nonstereoselective cross metathesis was addressed by development of “methylene-free” conditions. In general, the low stereoselectivity in cross enyne metathesis of alkenes and alkynes limits its utility in synthesis.¹⁵ Low selectivity was also evident in our initial work on the tandem dienyne metathesis.¹⁶ In the case of 1,3-cyclohexadiene synthesis, only the *Z*-alkene would lead to the ring-closed product. This problem led us to consider interconversion of vinyl carbene intermediates to produce more of the *Z*-intermediate, which would then give ring-closing metathesis. This process would produce more of the desired cyclohexadiene product. Our analysis led us to consider conditions that would favor interconversion of vinyl carbenes by omitting CH₂ sources. These conditions were expected to decelerate the rate of catalyst turnover, giving the isomeric vinyl carbene intermediates time to interconvert. Since there are no CH₂ sources in the reaction and no L_{*n*}Ru=CH₂ intermediates, we termed these conditions to be “methylene-free.”² The term is used to differentiate these conditions from typical cross metatheses, which had previously required the use of 1-alkene reactants. (However, the catalytic enyne metathesis mechanism is complex,¹⁷⁻¹⁹ and the hypothesis that methylene-free conditions permit the equilibration of vinyl carbene intermediates requires further experimentation.)

The procedure described here illustrates that the methylene-free conditions provide an effective ring synthesis of 1,3-cyclohexadienes. In the best cases, the cyclohexadienes are produced in greater than 80% yield (as assessed by NMR). The isolation procedure requires separation of oligomeric materials derived from polybutadiene. This procedure employs polybutadiene (PB) as the alkene reactant, yet similar results are obtained using 1,5-cyclooctadiene (1,5-COD) as the alkene. In the 20-mmole scale procedure above using 4 equiv of 1,5-COD (8 alkene equivalents), 61% yield of the corresponding 1,3-cyclohexadiene was obtained (in comparison to 65% with 8 equiv PB). However, use of fewer equivalents of polybutadiene (4 equiv) led to incomplete conversion of alkyne reactant (64% conversion of propargyl benzoate as assessed by ¹H NMR comparison to the mesitylene internal standard).

Table 1 shows results using 4 equiv of 1,5-COD in place of polybutadiene on a 1-mmole scale. On the smaller scale, catalyst loading was not optimized lower than 5 mole %, though it is anticipated that catalyst loading can be decreased during scale-up.²⁰ We have found that either 8 equiv PB or 4 equiv 1,5-COD can be used with equal efficiency.

Table 1. Ring Synthesis by Methylene-Free Enyne Metathesis^{a,b}

entry	alkyne	X	Y	yield(NMR)	yield
1		OBz	-	83	71
2		OTBDPS	-	62	51
3		OCH ₂ Ph	-	69	59
4		CH ₃	OBz	88	74
5		CH ₂ Ph	OAc	80	66
6 ^a		OC(O)β-Nap-	-	50	41
7		N(Ts)Boc	-	77	62
8		CO ₂ Et	-	72	68
9 ^{c,d}		ONap	-	49	42
10		Cl	-	62	48

(a) All reactions were conducted on a 1 mmole scale and used the Grubbs second generation catalyst. (b) A solution of alkyne (1 equiv) and 1,5-COD (2 equiv) was added to a solution of ruthenium catalyst (5 mol %) and 1,5-COD (2 equiv) in refluxing CH₂Cl₂ over a period of 4 h. (c) Incomplete conversion. (d) 10 mol % ruthenium catalyst was used.

A variety of terminal alkynes participated efficiently in this reaction. Esters at the propargylic and homopropargylic position were well tolerated (entries 1, 4, 5, 6). Protected propargyl ethers gave reasonable isolated yields (entries 2, 3). Nitrogen-containing homopropargylic functionality was tolerated if suitably protected (entry 7), and a remote ester posed no difficulty (entry 8). The more remote naphthoate ester required higher catalyst loading and still proceeded to only partial conversion (entry 9). This is presumably due to a coordination problem in the intermediate vinyl carbenes, which may both slow the reaction and result in catalyst decomposition. Coordinating ethers in the homopropargylic position were similarly not well tolerated (examples are not shown in the Table). For

example, homopropargyl benzyl ether gave only 50% conversion to product using 15 mole % catalyst loading. Since internal alkenes coordinate more weakly to metals than 1-alkenes, the putative slow step, vinyl carbene reaction with alkene, is slower than a typical enyne metathesis involving 1-alkenes. As a result, the reaction proves more sensitive to potentially coordinating functional groups than typical ring-closing alkene or enyne metathesis reactions. In these unusual cases, higher catalyst loading is needed. To elucidate the complications in these cases, further studies will be needed. Methylene-free conditions have also been used for the ring expansion of cyclopentene to give 1,3-cycloheptadienes.²¹

In conclusion, a practical synthesis of 1,3-cyclohexadienes is possible from simple, readily available unsaturated reactants. The optimal 20-mmole scale procedure employs the second generation Grubbs carbene as a functional group tolerant catalyst. A moderately low catalyst loading was achieved despite the demands of a slow intermolecular reaction. The key to this method is the use of methylene-free conditions, achieved with either polybutadiene or 1,5-cyclooctadiene as the alkene.

1. Department of Chemistry, 572 Natural Sciences Complex, University at Buffalo, The State University of New York, Amherst, NY 14260-3000, (716) 645-6800 x2201, email: diver@buffalo.edu.
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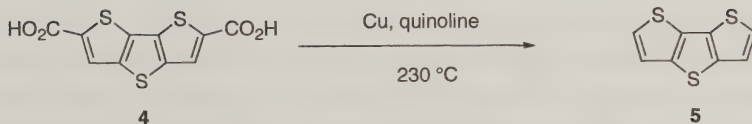
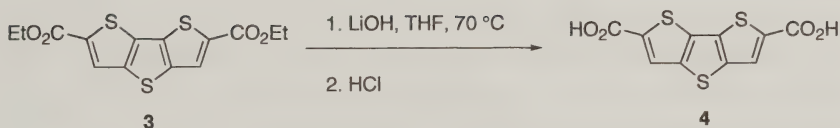
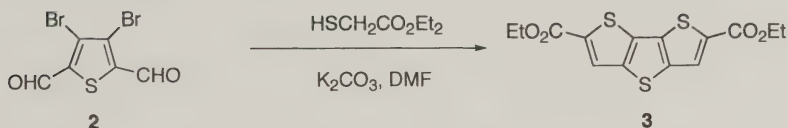
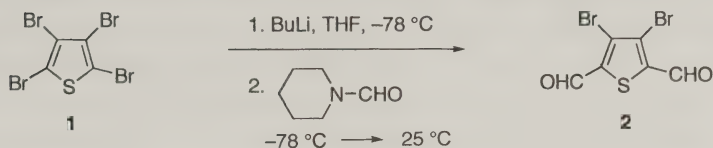
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

Propargyl alcohol: 2-Propyn-1-ol; (107-19-7)
 Benzoyl chloride; (98-88-4)
 Triethylamine: *N,N*-Diethylethanamine; (121-44-8)
 DMAP: 4-Pyridinamine, *N,N*-dimethyl-; (1122-58-3)
 Propargyl benzoate: 2-Propyn-1-ol, benzoate; (6750-04-5)
cis-Polybutadiene; (40022-03-5)
 Grubbs' second generation catalyst: Ruthenium [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro(phenylmethylene)(tricyclohexylphosphine); (246047-72-3)
 Ethyl vinyl ether: Ethene, ethoxy-; (109-92-2)

SYNTHESIS OF DITHIENO[3,2-*b*:2',3'-*d*]THIOPHENE



Submitted by Joseph Frey, Steffen Proemmel, Michael A. Armitage, and Andrew B. Holmes.¹

Checked by Ryo Takita and Masakatsu Shibasaki.

1. Procedure

A. 3,4-Dibromo-2,5-diformylthiophene (2). An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a magnetic stir bar, a low-temperature thermometer, a rubber septum and a three-way stopcock to which an argon balloon is attached. Under a gentle flow of argon, the flask is charged with tetrabromothiophene **1** (16.0 g, 40.0 mmol) (Note 1) and freshly-distilled tetrahydrofuran (200 mL) (Note 2). The solution is cooled

with a dry ice/2-propanol bath to an internal temperature of less than $-65\text{ }^{\circ}\text{C}$ and a solution of butyllithium (50 mL, 1.6 M in hexanes, 80 mmol, 2 equiv) is added via syringe. The addition proceeds at a rate that keeps the internal temperature below $-60\text{ }^{\circ}\text{C}$, usually taking 30 min. When the addition is complete, the brown solution is stirred at about $-70\text{ }^{\circ}\text{C}$ for 30 min. Dry *N*-formylpiperidine (10 mL, 90 mmol, 2.25 equiv) (Note 3) is added quickly (in about 10 s) by syringe to the reaction mixture, which is then allowed to warm slowly to ambient temperature overnight. The reaction mixture is cooled to $0\text{ }^{\circ}\text{C}$ in an ice-water bath, and hydrochloric acid (100 mL, 6 M) is added slowly to the reaction mixture, causing a yellow precipitate to form. The mixture is stirred at $0\text{ }^{\circ}\text{C}$ for 45 min then filtered immediately under vacuum through a sintered-glass funnel. The solid is washed with water (150 mL) and dried in the funnel under vacuum for 30 min before being dried further in a vacuum dessicator (25 mmHg, overnight, silica gel dessicant with moisture indicator) to give the crude dialdehyde **2** (8.8 g, 74%) (Notes 4, 5). The material is carried forward without further purification.

B. *Dithieno[3,2-b:2',3'-d]thiophene-2,6-dicarboxylic acid diethyl ester* (**3**). In an oven-dried 500-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar, nitrogen inlet and rubber septum, 3,4-dibromo-2,5-diformylthiophene **2** (8.0 g, 26.9 mmol) is suspended in anhydrous *N,N*-dimethylformamide (250 mL) (Note 6). Anhydrous potassium carbonate (9.65 g, 69.8 mmol, 2.6 equiv) (Note 7) and ethyl 2-mercaptoacetate (6 mL, 55 mmol, 2.05 equiv) are added to the slurry, causing a slight exotherm, and the reaction mixture is stirred under nitrogen at ambient temperature for three days. The dark solution is poured into a beaker containing 500 mL of water stirred with a magnetic stir bar, and a yellow precipitate forms. The aqueous suspension is extracted with dichloromethane (3 x 250 mL). The red organic extracts are combined, washed with brine (4 x 500 mL) and dried over anhydrous magnesium sulfate (Note 8). After filtration through fluted filter paper, the solvents are evaporated on a rotary evaporator and a yellow solid begins to form. When the volume of solvent remaining is about 100 mL, the solid is filtered under vacuum on a Büchner funnel, washed with water (100 mL) and dried in a vacuum dessicator (7–8 mmHg, overnight, silica gel dessicant with moisture indicator) to give the crude diester **3** (6.8 g, 74%) (Note 9). The material is carried forward without further purification.

C. *Dithieno[3,2-b:2',3'-d]thiophene-2,6-dicarboxylic acid* (**4**). In a 500-mL, one-necked, round-bottomed flask equipped with a magnetic stir

bar and reflux condenser under a static argon atmosphere (Note 10), dithieno[3,2-*b*:2',3'-*d*]thiophene-2,6-dicarboxylic acid diethyl ester **3** (5.00 g, 14.7 mmol) is suspended in tetrahydrofuran (75 mL). An aqueous solution of 1 M lithium hydroxide (75 mL, 75 mmol, 5.1 equiv.) is added (Note 11), causing the color of the suspension to change from yellow to terracotta. The mixture is heated to 70 °C (oil bath temperature) and stirring is maintained at this temperature for 4 h to give an orange solution. The solvent is evaporated on a rotary evaporator until the volume remaining is about 75 mL. A small amount of precipitate is observed. The solution is acidified with 1 M hydrochloric acid (100 mL) to give a white precipitate with some slight foam. The solid is filtered slowly under vacuum on a Büchner funnel (Note 12) and washed sequentially with water (200 mL), methanol (100 mL) and diethyl ether (100 mL). Finally, the solid is dried overnight in a high vacuum oven (40 °C, approx. 0.02 mmHg) to afford the crude diacid **4** (3.8 g, 91%) (Notes 13, 14). The material is carried forward without further purification.

D. *Dithieno[3,2-*b*:2',3'-*d*]thiophene (5)*. In a 50-mL, two-necked, round-bottomed flask equipped with a magnetic stir bar, a reflux condenser and an internal thermometer, dithieno[3,2-*b*:2',3'-*d*]thiophene-2,6-dicarboxylic acid **4** (3.80 g, 13.4 mmol) and copper powder (0.81 g, 12.7 mmol, 0.95 equiv) (Note 15) are suspended in quinoline (25 mL). The mixture is heated to reflux at 230 °C for 1 h using a heating mantle. Petroleum ether (40–60) is added to the cooled reaction mixture and the organic layer is decanted into a 500-mL separatory funnel (Note 16). This process is repeated several times until the volume of the organic layer is about 150 mL. The organic phase is washed with 2 M hydrochloric acid (3 x 70 mL) and brine (3 x 100 mL). The organic layer is then dried over anhydrous magnesium sulfate, filtered through a fluted filter paper and the solvent is removed on a rotary evaporator to give a pale yellow oil. The residue is dissolved in a small amount of dichloromethane and filtered through a short (about 8 cm length x 5.5 cm diameter) column of silica (Note 17), using petroleum ether (40-60) as eluent. The eluent is concentrated on a rotary evaporator to give a white crystalline solid. The solid is recrystallized by dissolving in 2 mL of dichloromethane at 30 °C, adding methanol dropwise at a rate of one drop every 5 seconds to the solution until it becomes cloudy (about 5 mL), adding another drop of dichloromethane to remove the cloudiness and allowing the solution to cool to ambient temperature for 30 min. The resulting crystals are collected under vacuum on a Büchner funnel, washed with ice-cold methanol (10 mL), dried

in the funnel under vacuum and transferred to an appropriate vial to be further dried in a vacuum dessicator (25 mmHg, overnight, silica gel dessicant with moisture indicator) to give the purified dithieno[3,2-*b*:2',3'-*d'*]thiophene **5** (1.9 g, 72%) (Note 18).

2. Notes

1. Tetrabromothiophene (99+%) and ethyl 2-mercaptoacetate (99%) were purchased from Acros Organics and were used as received. Butyllithium (1.6 M solution in hexanes) was purchased from Aldrich.

2. Tetrahydrofuran was distilled from sodium benzophenone ketyl.

3. *N*-Formylpiperidine (98%) was purchased from Lancaster Synthesis and dried over activated 4 Å molecular sieves before use. The molecular sieves were activated in a round-bottomed flask that was heated in a microwave oven (50 W) at full power for 5 min, then evacuated under vacuum (7–8 mmHg) on a vacuum line for 5 min while being allowed to cool to room temperature. This procedure was repeated three times. The flask was sealed with a three-way cock until the activated sieves were used. *N*-Formylpiperidine was dried by standing in a sealed bottle over activated MS 4 Å at room temperature overnight. The submitters found that some mono-aldehyde [¹H NMR (400 MHz, CDCl₃) δ: 7.75 (s, 1 H), 9.94 (s, 1 H)] was formed if the *N*-formylpiperidine was insufficiently dry.

4. All analytical thin layer chromatography analyses (TLC) were carried out on Merck pre-coated 0.25 mm thick plates of silica gel 60 F₂₅₄. The plates were visualized with 254 nm UV light followed by a phosphomolybdic acid solution (10% w/v in MeOH) stain.

5. The submitters report yields that range from 69–80%. The crude product has the following properties; *R_f* = 0.30 (5:1, hexane:ethyl acetate); mp 225 °C (sub.) (lit.,² 227 °C); IR (solid): 1663 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 10.07 (s, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ: 123.7, 142.3, 183.3; LRMS (ESI) *m/z* 425 [M + 2(*i*-PrOH) + Li], 723 [2M + 2(*i*-PrOH) + Li]; Anal. Calcd for C₆H₂O₂SBr₂: C, 24.19; H, 0.68. Found: C, 24.25; H, 0.90.

6. Anhydrous *N,N*-dimethylformamide (99.8%) and lithium hydroxide monohydrate were purchased from Aldrich Chemical Company and were used as received.

7. Anhydrous potassium carbonate (>99%) was purchased from Wako Pure Chemical Industries and was used as received. In the submitter's

case, anhydrous potassium carbonate (>99%) was purchased from Fisher Scientific UK and was used as received.

8. Anhydrous magnesium sulfate (99%) was purchased from Wako Pure Chemical Industries and was used as received. In the submitter's case, anhydrous magnesium sulfate (99%) was purchased from BDH and was used as received.

9. The submitters report yields that range from 69–71%. The crude product has the following properties; $R_f = 0.40$ (5:1, hexane:ethyl acetate); mp 189–190 °C (lit.,³ 196 °C); IR (solid): 2983, 2934, 1715, 1691, 1228 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.41 (t, $J = 7.5$ Hz, 6 H), 4.40 (q, $J = 7.5$ Hz, 4 H), 8.00 (s, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.5, 61.8, 126.8, 135.4, 136.0, 143.4, 162.2; LRMS (ESI (+)) m/z 363 [$\text{M} + \text{Na}$], 703 [$2\text{M} + \text{Na}$]; Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{O}_4\text{S}_3$: C, 49.39; H, 3.55. Found: C, 49.23; H, 3.44.

10. A static inert atmosphere was provided by attaching a three-way cock with an argon balloon at the top of the condenser. The flask was flushed with argon after the addition of reagents.

11. The aqueous solution of lithium hydroxide was prepared by dissolving 3.15 g (75 mmol) of lithium hydroxide monohydrate (Aldrich) in 75 mL of distilled water.

12. Filter paper purchased from Toyo Roshi Kaisha (No.2) was used. The checkers observed some clogging or a partial leak of a small amount of solid. The submitters used Whatman filter paper No. 54 (hardened, ashless).

13. The submitters report yields that range from 95–96%. The crude product has the following properties; mp >300 °C; IR (solid) cm^{-1} : 3083–2557 br, 1692, 1661; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 8.18 (s, 2 H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 127.7, 134.3, 137.0, 143.8, 163.3. LRMS (ESI (-)) m/z 283 [$\text{M}-\text{H}$], 567 [$2\text{M}-\text{H}$]; Anal. Calcd for $\text{C}_{10}\text{H}_4\text{O}_4\text{S}_3$: C, 42.24; H, 1.42. Found: C, 42.32; H, 1.61.

14. Because the product is only soluble in DMSO, TLC analysis gives $R_f = 0$ in MeOH. TLC may therefore be used to verify the loss of starting material but will not confirm the formation of the product.

15. Copper powder (99+%, irregular 300 mesh) and quinoline (98+%) were purchased from Lancaster Synthesis and were used as received.

16. The organic phases are decanted to separate the product from the insoluble copper salts.

17. Column chromatography was performed using silica gel (Merck silica gel 60 (230–400 mesh)).

18. The submitters report yields that range from 59–71%. The purified product has the following properties; $R_f = 0.33$ (hexane); mp 66–67 °C (lit.,⁴ 66–67 °C); IR (solid) cm^{-1} : 3096, 3074, 1464, 1357; ^1H NMR (500 MHz, CDCl_3) δ : 7.29 (d, $J = 5.5$ Hz, 2 H), 7.36 (d, $J = 5.5$ Hz, 2 H); ^{13}C NMR (126 MHz, CDCl_3) δ : 120.9, 125.9, 131.0, 141.7; LRMS (ESI (+)) m/z 305 [M+Ag], 501 [2M+Ag]; Anal. Calcd for $\text{C}_8\text{H}_4\text{S}_3$: C, 48.95; H, 2.05. Found: C, 48.69; H, 2.20.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

In recent years much interest has been directed to dithieno[3,2-*b*:2',3'-*d*]thiophene (DTT) **5** as a unit in semiconducting organic materials.^{5–8} In particular, the dimer α,α' -bis(dithieno[3,2-*b*:2',3'-*d*]thiophene)⁹ and its derivatives¹⁰ have been used as high mobility semiconductors in field-effect transistors, with field-effect mobilities of up to $0.05 \text{ cm}^2\text{V}^{-1}\text{s}^{-1}$ being recorded.⁹

The most recent syntheses of DTT were reported in 2002, by Hellberg and coworkers¹¹ in Sweden, and by Holmes and Frey³ in Cambridge, UK. Both of these routes showed improvements over the previous method, which was published by De Jong in 1971.⁴ Although the route reported by Hellberg appears to be more convenient in having fewer synthetic steps, the present method has several advantages. Each of the intermediates is a solid that requires no purification before taking forward, thus providing a quick and efficient synthetic route. The final product, DTT **5**, is quickly purified by flash column chromatography followed by recrystallization. Finally, the synthesis may be carried out on scales of over 30 g, although the lithiation step is limited on a laboratory scale due to the difficulty in cooling large-scale glassware.

DTT can be brominated in the 2- and 6- positions with NBS. This dibromide can be used in a variety of cross coupling reactions to form

interesting conjugated oligomers and polymers. In addition, a novel silylation procedure can introduce TMS groups to the 3- and 5- positions.³

1. Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, U.K. and School of Chemistry, University of Melbourne, Vic. 3010, Australia.; Bio21 Institute, University of Melbourne, Vic. 3010, Australia.
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

Tetrabromothiophene; (3958-03-0)

N-Formylpiperidine: 1-Piperidinecarboxaldehyde; (2591-86-8)

3,4-Dibromo-2,5-diformylthiophene: 2,5-Thiophenedicarboxaldehyde, 3,4-dibromo-; (25373-20-0)

Ethyl 2-mercaptoacetate: Acetic acid, mercapto-, ethyl ester; (623-51-8)

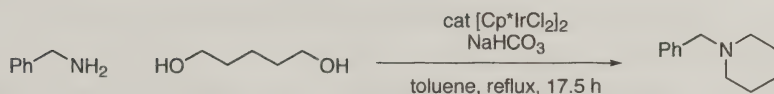
Dithieno[3,2-b:2',3'-d]thiophene-2,6-dicarboxylic acid diethyl ester;

(502764-52-5)

Dithieno[3,2-b:2',3'-d]thiophene-2,6-dicarboxylic acid; (502764-53-6)

Dithieno[3,2-b:2',3'-d]thiophene; (593-75-7)

IRIDIUM-CATALYZED *N*-HETEROCYCLIZATION OF PRIMARY AMINES WITH DIOLS: *N*-BENZYLPIPERIDINE



Submitted by Ken-ichi Fujita,^{1a} Youichiro Enoki, and Ryohei Yamaguchi.^{1b}
Checked by Gustavo Moura-Letts and Dennis P. Curran.^{1c}

1. Procedure

N-Benzylpiperidine (Note 1). A 100-mL, two-necked, round-bottomed flask fitted with a magnetic stirring bar, a rubber septum, and a reflux condenser with a bubbler-sealed outlet is charged with di- μ -chloro-dichlorobis(η^5 -pentamethylcyclopentadienyl)diiridium [Cp*IrCl₂]₂ (199 mg, 0.25 mmol) (Note 2) and sodium bicarbonate (41 mg, 0.48 mmol) (Note 3) under an argon atmosphere. Addition of 10 mL of toluene (Note 4) by syringe to the flask affords an orange suspension. Benzylamine (10.70 g, 10.91 mL, 99.86 mmol) (Note 5) is added by syringe through the rubber septum over 10 sec. During the addition, the color of the suspension changes to yellow. Then 1,5-pentanediol (10.39 g, 10.45 mL, 99.76 mmol) (Note 5) is added by syringe through the septum over 30 sec. Under an argon flow, the rubber septum is replaced with a glass stopper. The black suspension (Note 6) is heated at reflux in an oil bath (oil bath temperature: 120 °C) for 17.5 h, then the reaction mixture is cooled to room temperature (Note 7). The reflux condenser is removed, and a short-path vacuum distillation apparatus is mounted to the flask. Distillation at 21.0 mmHg yields a fraction boiling between 123–125 °C; the clear, very pale yellow liquid is *N*-benzylpiperidine (14.20–14.30 g, 81–82% based on 1,5-pentanediol) (Notes 8, 9).

2. Notes

1. This is a modification of a published procedure.²
2. The submitters prepared the iridium complex di- μ -chloro-dichlorobis(η^5 -pentamethylcyclopentadienyl)diiridium according to

the literature method.³ They also report that the commercially available complex from Aldrich Chemical Company, Inc. or Strem Chemicals, Inc. can be substituted. The checkers purchased the catalyst from Strem.

3. Sodium bicarbonate (EP) was purchased from Wako Pure Chemical Industries, Ltd. (submitters) or Fisher Scientific (checkers) and used as received.

4. Toluene (GR) was purchased from Wako Pure Chemical Industries, Ltd. (submitters) or Aldrich (checkers) and distilled from sodium benzophenone ketyl under an argon atmosphere before use.

5. Benzylamine (GR, >99%) and 1,5-pentanediol (EP, >97%) were purchased from Tokyo Kasei Kogyo Co., Ltd. (submitters) or Aldrich (checkers) and used as received.

6. The submitters reported that the mixture remained yellow, but the checkers observed that it turned black after about 5 min.

7. At this time, a small quantity of water was observed in the bottom of the flask.

8. The submitters reported that the distillate was colorless. The checkers observed that the clear, very pale yellow liquid could be redistilled to provide a clear, colorless liquid, if desired. Alternatively, in a separate run where special care was taken to collect only clear distillate, 13.30 g (76%) product was obtained.

9. The spectral data and elemental analysis are as follows: ¹H NMR (300 MHz, CDCl₃) δ: 1.42 (m, 2 H), 1.56 (m, 4 H), 2.36 (m, 4 H), 3.46 (s, 2 H), 7.31–7.23 (m, 5 H); ¹³C NMR (75 MHz, CDCl₃) δ: 24.3, 25.9, 54.4, 63.8, 126.7, 127.9, 129.0, 138.6; IR (thin film) 3062, 2934, 2852, 2684, 1493, 1369, 1154, 1113 cm⁻¹; EIMS *m/z*: 91(100), 175(95), 98(92), 84(91), 65(75), 176(58). Purity (>99.5%) was assessed by Gas Chromatography (GC) with a retention time (*R_t*) of 11.16 min: (Agilent 19091Z-413E, HP-1 Methyl siloxane, 0.32mm x 30m x 0.25μm; temperature 50 °C, ramp 10°/min to 350 °C).

Safety and Waste Disposal Information

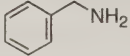
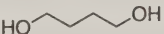
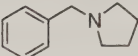
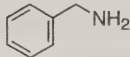
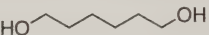
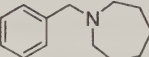
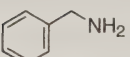
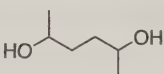
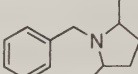
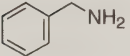
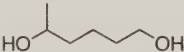
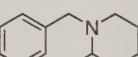
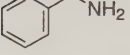
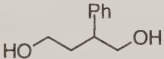
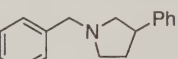
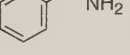
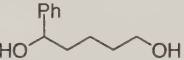
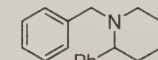
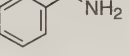
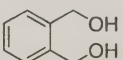
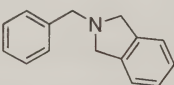
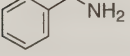
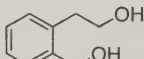
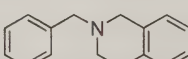
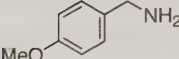
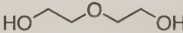
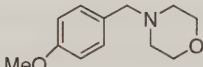
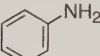
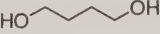
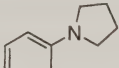
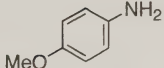
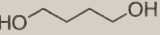
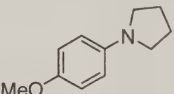
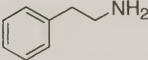
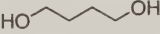
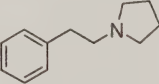

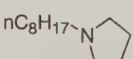
All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

N-Heterocyclic compounds are important intermediates in medicinal chemistry, material chemistry, and synthetic organic chemistry. In particular, pyrrolidine, piperidine and morpholine derivatives are present in large classes of biologically active natural products. For the past several decades, much effort has been devoted to development of efficient methods for the synthesis of these *N*-heterocycles. Recently, a variety of transition metal-catalyzed reactions for the synthesis of *N*-heterocyclic compounds have been disclosed and reviewed.^{4,5} From an environmental point of view, *N*-heterocyclization of primary amines with diols is an attractive method because an *N*-heterocyclic product can be obtained from easily available starting materials in one pot without generation of wasteful or harmful byproducts (H_2O is the only byproduct). Although some ruthenium-catalyzed systems for *N*-heterocyclization of primary amines with diols have been reported, most of them require high reaction temperature ($>150\text{ }^\circ\text{C}$) and applicable substrates are rather restricted.⁶⁻⁹

The method outlined here represents a convenient and environmentally benign *N*-heterocyclization of primary amines with diols catalyzed by a $\text{Cp}^*(\text{C}_5\text{Me}_5)$ iridium complex. The reaction can be conducted under relatively mild conditions (reflux in toluene as a solvent), and it does not generate any wasteful byproducts. Additional examples of the $[\text{Cp}^*\text{IrCl}_2]_2$ -catalyzed *N*-heterocyclization of primary amines with diols are shown in the Table.² Using this protocol, a variety of pyrrolidine, piperidine, and morpholine derivatives can be synthesized in good to excellent yields. A seven-membered cyclic amine (azepane) can be also synthesized in a satisfactory yield (entry 2).

Table. Cp*Ir Complex-Catalyzed *N*-Heterocyclization of Primary Amines with a Variety of Diols^a

entry	amine	diol	cat (%Ir)	yield ^b (%)	product
1			1.0	72	
2 ^c			2.0	73	
3 ^d			1.0	94 ^e	
4			1.0	79	
5			2.0	90	
6			4.0	78 ^f	
7 ^{g,h}			2.0	63	
8			2.0	76	
9			2.0	76	
10 ^{i,j}			5.0	70	
11 ⁱ			5.0	90	
12			4.0	73	
13	$n\text{-C}_8\text{H}_{17}\text{NH}_2$		4.0	81 ^f	

^aThe reaction was carried out at 110 °C for 17 h with amine (3.0 mmol), diol (2.0 mmol), {Cp*IrCl₂}₂ (1.0–5.0 % Ir), and NaHCO₃ (same number of equiv as Ir catalyst) in toluene (1 mL). ^bIsolated yield.

^cToluene (3 mL) was used. ^dNa₂CO₃ was used as base. ^eCis/trans = 73/27 (determined by ¹H NMR analysis). ^fGC yield. ^gAmine (2.0 mmol) was used. ^hBase was not added. ⁱReaction temperature was 130 °C. ^jReaction time was 40 h.

1. a) Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan; email: fujitak@kagaku.mbox.media.kyoto-u.ac.jp
b) email: yama@kagaku.mbox.media.kyoto-u.ac.jp c) Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, email: curran@pitt.edu
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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

Di- μ -chloro-dichlorobis(η^5 -pentamethylcyclopentadienyl)diiridium
 [Cp*IrCl₂]₂ Iridium, di- μ -chlorodichlorobis[(1,2,3,4,5- η)-1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl]di-; (12354-84-6)
 1,5-Pentanediol; (111-29-5)
 Benzylamine: Benzenemethanamine; (100-46-9)
 N-Benzylpiperidine: Piperidine, 1-(phenylmethyl)-; (2905-56-8)

CUMULATIVE AUTHOR INDEX FOR VOLUMES 80-83

This index comprises the names of contributors to Volumes **80**, **81**, **82**, and **83**. For authors of previous volumes, see either indices in Collective Volumes I through X, or the single volume entitled *Organic Syntheses, Collective Volumes I-VIII, Cumulative Indices*, edited by J. P. Freeman.

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CUMULATIVE SUBJECT INDEX FOR VOLUMES 80-83

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The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to Chemical Abstracts nomenclature, accompanied by its registry number in parentheses. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

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4-Amino-1-*tert*-butyloxycarbonylpiperidine-4-carboxylic acid: 1,4-Piperidine dicarboxylic acid, 4-Amino-, 1-(1,1-dimethylethyl)ester (9); (183673-71-4), **81**, 216

(1*S*,2*R*)-(-)-*cis*-1-Amino-2-indanol: 1*H*-Inden-2-ol, 1-amino-2,3-dihydro-, (1*S*,2*R*)-; (126456-43-7) **82**, 34, 157; **83**, 131

(2*S*)-(-)-3-*exo*-Aminoisoborneol: 3-Amino-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ol; (417199-73-7) **82**, 87

4-Amino-2,2,6,6-tetramethylpiperidine: 4-Piperidinamine, 2,2,6,6-tetramethyl- (9); (36768-62-4) **82**, 80

Ammonia; (7664-41-7), **80**, 31; **82**, 157

Ammonium carbonate: Carbonic acid, diammonium salt (8,9); (506-87-6), **81**, 215

Ammonium chloride (NH₄Cl) (9); (12125-02-9), **81**, 188

p-Anisidine: Benzenamine, 4-methoxy-; (104-94-9), **80**, 160

Antimony pentachloride; Antimony chloride; (7647-18-9) **82**, 1

Arylboronate synthesis, **81**, 89, 134

Asymmetric hydrogenation, **81**, 178

Aziridine Formation; **82**, 170

Benzaldehyde; (100-52-7), **80**, 160; **83**, 5

Benzamide hydrochloride: Benzenecarboximidamide, monohydrochloride (9); (1670-14-0), **81**, 105

Benzenesulfonyl chloride; (931-59-9), **81**, 244, 246

Benzenesulfinic acid, sodium salt: Sodium benzenesulfinate; (873-55-2) **83**, 24

Benzenethiol; Thiophenol; (108-98-5), **80**, 184

(4*S*)-2-(BENZHYDRYLIDENAMINO)PENTANEDIOIC ACID, 1-*tert*-BUTYL ESTER-5-METHYL ESTER: L-Glutamic acid, *N*-(diphenylmethylene)-, 1-(1,1-dimethylethyl)-5-methyl ester; (212121-62-5), **80**, 38

Benzil: Ethanedione, diphenyl-; (134-81-6) **82**, 10; **83**, 38

rac-Benzoin: Ethanone, 2-hydroxy-1,2-diphenyl-; (19-53-9) **82**, 10

Benzonitrile; (100-47-0), **81**, 123

1,4-Benzoquinone: 2,5-Cyclohexadiene-1,4-dione; (106-51-4), **80**, 233; **82**, 1

Benzoyl chloride; (98-88-4) **83**, 200

2-(BENZOYLOXYMETHYL)-1,3-CYCLOHEXADIENE: 1,5-Cyclohexadiene-1-methanol, benzoate; (333310-22-8)

2 α -BENZYLOXY-8-OXABICYCLO[3.2.1]OCT-6-EN-3-ONE: (238757-83-0)

(1*S*, 2*S*)-1-BENZOYLOXY-2-BROMOCYCLOHEXANE; Cyclohexanol, 2-bromo-, benzoate, (1*S*, 2*S*)-; (222851-77-6) **83**, 70

4-Benzoyloxymorpholine; (5765-65-1) **83**, 31

Benzyl alcohol: Benzenemethanol; (100-51-6) **82**, 120

Benzylamine: Benzenemethanamine; (100-46-9), **81**, 262; **82**, 170; **83**, 217

(2*S*, 6*S*)-4-Benzyl-1,7-bis(trifluoromethylsulfonyl)-2,6-diisopropyl-1,4,7-triazaheptane: *N,N'*-[[[(Phenylmethyl)imino]bis[(1*S*)-1-(1-methylethyl)-2,1-ethanediyl]]bis[1,1,1-trifluoro]-methanesulfonamide; (200351-80-0) **82**, 170

N-Benzylidene-*p*-anisidine: Benzenamine, 4-methoxy-*N*-(phenylmethylene)-; (783-08-4), **80**, 160

N-Benzylidene-benzylamine *N*-oxide; Benzenemethanamine, *N*-(phenylmethylene)-, *N*-oxide; (3376-26-9), **81**, 204

trans-2-BENZYL-1-METHYLCYCLOPROPAN-1-OL; 1-Cyclopropanol, 1-methyl-2-phenylmethyl-; **80**, 111

N-BENZYL-4-PHENYLBUTYRAMIDE: Benzenebutanamide, *N*-(phenylmethyl)-; (179923-27-4), **81**, 262

N-BENZYLPIPERIDINE: Piperidine, 1-(phenylmethyl)-; (2905-56-8) **83**, 217

Benzyltriethylammonium chloride; Benzenemethanaminium, *N,N,N*-triethyl-, chloride; (56-37-1) **83**, 184

BICYCLO[2.2.1]HEPT-5-ENE-2-ENDO-CARBOXYLIC ACID, 3-ENDO-BENZYLOXYCARBONYL, (2*R*, 3*S*)-: Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid, mono(phenylmethyl) ester, (1*R*, 2*S*, 3*R*, 4*S*)-; (581100-26-7) **82**, 120

endo-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride: 4,7-Methanoisobenzofuran-1,3-dione, 3*a*, 4, 7, 7*a*-tetrahydro-, (3*aR*, 4*S*, 7*R*, 7*aS*)-rel-; (129-64-6) **82**, 120

BICYCLO[3.1.0]HEXAN-1-OL; (7422-09-5), **80**, 111

(*R*)-BINAP: Phosphine, (1*R*)-[1,1: binaphthalene]-2,2'-diayhdriis (diphenyl)-; (76189-55-4) **81**, 178

Bis(2-bromoethyl) ether: Ethane, 1,1'-oxybis[2-bromo-; (5414-19-7) **82**, 87

2,2-Bis(chloromethyl)-5,5-dimethyl-1,3-dioxane: 1,3-Dioxane, 2,2-bis(chloromethyl)-5,5-dimethyl-; (133961-12-3), **80**, 144

(*S,S*)-1,2-BIS-(*tert*-BUTYLMETHYLPHOSPHINO)ETHANE ((*S,S*)-*t*-Bu-BISP*) **82**, 22

Bis (tri-*tert*-butylphosphine)palladium: Palladium, bis[tris(1,1-dimethylethyl)phosphine]- (9); (53199-31-8), **81**, 63

(*R,R*)-(-)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II): Cobalt, [[2,2'-[(1*R*, 2*R*)-1,2-cyclohexanediylbis[(nitrilo- κ N)methylidyne]]bis[4,6-bis(1,1-dimethylethyl)phenolato- κ O]](2-)-], (SP-4-2)-; (176763-62-5) **83**, 162

Bis(η^4 -1,5-cyclooctadiene)-di- μ -methoxy-diiridium(I) ([Ir(OMe)(COD)]₂): Bis[(1,2,5,6- η)-1,5-cyclooctadiene]di- μ -methoxydiiridium; (12148-71-9) **82**, 126

(-)-(*S,S*)- BIS(4-ISOPROPYLOXAZOLINE: Oxazole, 2,2'-(1-methylethylidene)bis[4,5-dihydro-4-(1-methylethyl)-, (4*S*, 4'*S*)-; (131833-92-6)

Bismuth bromide: Bismuthine, tribromo-; (7787-58-8) **83**, 155

Bis(pinacolato)diboron: 4,4,4',4',5,5,5',5'-octamethyl-2,2'-Bi-1,3,2-dioxaborolane; (73183-34-3) **82**, 126

2,2-Bispyrrolidine; 2,2-Bipyrrolidine; (74295-58-2) **83**, 121

(*R,R*)-2,2'-BISPYRROLIDINE: 2,2'-Bipyrrolidine, (2*R*,2'*R*)-; (137037-20-8) **83**, 121

(*R,R*)-2,2'-Bispyrrolidine•(L)-tartrate: 2,2'-Bipyrrolidine, (2*R*,2'*R*)-, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1)-; (137037-21-9) **83**, 121

(*S,S*)-2,2'-BISPYRROLIDINE: 2,2'-Bipyrrolidine, (2*S*,2'*S*)-; (124779-66-4) **83**, 121

(*S,S*)-2,2'-Bispyrrolidine•(D)-tartrate: 2,2'-Bipyrrolidine, [*S*-(*R**,*R**)]-, [*S*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1); (136937-03-6) **83**, 121

Bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride: Ruthenium, dichloro(phenylmethylene)bis(tricyclohexylphosphine)-; (172222-30-9), **80**, 85

3,5-Bis(trifluoromethyl)-acetophenone: 1-[3,5-Bis(trifluoromethyl)phenyl] ethanone; (30071-93-3) **82**, 115

3,5-Bis(trifluoromethyl)bromobenzene: 1-Bromo-3,5-bis(trifluoromethyl) benzene; (328-70-1) **82**, 115

3,5-BIS(TRIFLUOROMETHYL)ACETOPHENONE: (1-[3,5-Bis(trifluoromethyl)phenyl]-ethanone); (30071-93-3) **82**, 115

6,13-BIS(TRIISOPROPYLSILOXY)-9,10-DIMETHOXY[7]HELICENE BISQUINONE: Dinaphtho[2,1-*c*:1',2'-*g*]phenanthrene-1,4,15,18-tetrone, 9,10-dimethoxy-6,13-bis[[tris(1-methylethyl)silyl]oxy]-; (310899-14-0), **80**, 233

3,6-Bis[1-(triisopropylsiloxy)ethenyl]-9,10-dimethoxyphenanthrene: Silane,[(9,10-dimethoxy-3,6-phenanthrenediyl)bis(ethenylideneoxy)]tris(1-methylethyl)-; **80**, 233

Boc-diallylamine: Carbamic acid, di-2-propenyl-, 1,1-dimethylethyl ester; (151259-38-0) **80**, 85

N-Boc hydroxyproline methyl ester; 1,2-Pyrrolidinedicarboxylic acid, 4-hydroxy, 1-(1,1-dimethylethyl) 2-methyl ester, (2*S*,4*R*); (74844-91-0), **81**, 178

N-Boc-3-PYRROLINE: 1*H*-Pyrrole-1-carboxylic acid, 2,5-dihydro-, 1,1-dimethylethyl ester; (73286-70-1), **80**, 85

endo-1-BORNYLOXYETHYL ACETATE: Ethanol, 1-[[(*1R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl]oxy]-, acetate; (284036-61-9), **80**, 177

Borane-dimethylsulfide complex: Boron, trihydro[thiobis(methane)]-(*T*-4)-; (13292-87-0), **81**, 43

Borane-tetrahydrofuran: Boron, trihydro(tetrahydrofuran)-, (14044-65-6) **82**, 22

Boric acid: Boric acid (H₃BO₃); (10043-35-3), **81**, 262

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(*R,R*)-BozPHOS: Phospholane, 1-[2-[(2*R*,5*R*)-2,5-dimethyl-1-oxido-1-phospholanyl]phenyl]-2,5-dimethyl-, (2*R*,5*R*)-; (38132-66-8) **83**, 1, 5

Bromination, **80**, 75; **81**, 98, 99

Bromine; (7726-95-6), **80**, 75; **82**, 1, 30, 75, 179

Bromoacetonitrile; Acetonitrile, bromo-; (590-17-0), **80**, 207

2-Bromoanisole: Benzene, 1-bromo-2-methoxy-; (578-57-4) **82**, 69

Bromobenzene: Benzene, bromo-; (100-86-1), **80**, 57

trans-2-Bromocyclohexanol; (2425-33-4) **83**, 70

1-Bromo-2-propyne: 1-propyne, 3-bromo-; (106-96-7), **80**, 93

4-Bromo-1-butene: 1-Butene, 4-bromo-; (5162-44-7), **81**, 19

5-BROMOISOQUINOLINE: Isoquinoline, 5-bromo- (8,11); (34784-04-8), **81**, 98

5-BROMO-8-NITROISOQUINOLINE: Isoquinoline, 5-bromo-8-nitro-; (63927-23-1), **81**, 98

1-Bromononane: Nonane, 1-bromo-; (693-58-3), **81**, 33

2-Bromophenol: benzene, 2-bromo-1-hydroxy- (9); (95-56-7) **82**, 64
N-(2-Bromophenyl)acetamide; (614-76-6) **83**, 45
3-Bromopyridine: Pyridine, 3-bromo- (8, 9); (626-55-1), **81**, 89
3-Bromoquinoline: Quinoline, 3-bromo- (8, 9); (5332-24-1), **81**, 90
3-BROMOSALICYLALDEHYDE **82**, 64
3-Bromosalicylaldehyde: benzaldehyde, 2-hydroxy-3-bromo- (9); (1829-34-1) **82**, 64
N-Bromosuccinimide: Succinimide, *N*-bromo- (8); 2,5-Pyrrolidinedione, 1-bromo-; (128-08-5) **81**, 98, 99
3-Butenylmagnesium bromide: Magnesium, bromo-3-butenyl-(8,9); (7013-09-5), **81**, 17
(2*S*-*trans*)-2-*tert*-Butoxycarbonylacetyl-4-hydroxypyrrolidine-1-carboxylic acid, *tert*-butyl ester: 2-Pyrrolidinepropanoic acid, 1-[(1,1-dimethylethoxy)carbonyl]-4-hydroxy- β -oxo-, 1,1-dimethylethyl ester, [2*S*-*trans*]- (9); (167963-29-3), **81**, 178
(*R*)-(*N*-*tert*-BUTOXYCARBONYL)ALLYLGLYCINE: 4-Pentenoic acid, 2-[[[(1,1-dimethylethoxy)carbonyl]amino]-, (2*R*)-; (170899-08-8), **80**, 31
(3*R*,5*R*,6*S*)-4-*tert*-Butoxycarbonyl-5,6-diphenyl-3-(1'-prop-2'-enyl)morpholin-2-one: 4-Morpholinecarboxylic acid, 2-oxo-5,6-diphenyl-3-(2-propenyl)-, 1,1-dimethylethyl ester, [3*R*-(3*a*,5*b*,6*b*)]-; (143140-32-3), **80**, 31
2(*S*)-(β -*tert*-BUTOXYCARBONYL- α -(*R*)-HYDROXY)ETHYL-4(*R*)-HYDROXYPYRROLIDINE-1-CARBOXYLIC ACID, *tert*-BUTYL ESTER: (2-Pyrrolidinepropanoic acid, 1-[(1,1-dimethylethoxy)carbonyl]- β ,4-dihydroxy-, 1,1-dimethylethyl ester, [2*S*-[2 α (*S**),4*b*]]-; (167963-30-6), **81**, 178
2(*S*)-(β -*tert*-BUTOXYCARBONYL- α -(*S*)-HYDROXY)ETHYL-4(*R*)-HYDROXYPYRROLIDINE-1-CARBOXYLIC ACID, *tert*-BUTYL ESTER, **81**, 178
N-(*tert*-BUTOXYCARBONYL)- L-iodoALANINE METHYL ESTER: L-Alanine, *N*-[(1,1-dimethylethoxy)carbonyl]-3-iodo-, methyl ester; (93267-04-0), **81**, 77
N-(*tert*-BUTOXYCARBONYL)- L-4-(METHOXYCARBONYL)PHENYL]ALANINE METHYL ESTER: L-Phenylalanine, *N*-[(1,1-dimethylethoxy)carbonyl]-4-(methoxycarbonyl)-, methyl ester (9); (160168-19-4), **81**, 77
tert-Butoxycarbonyl- L-proline: 1,2-Pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl)ester, (*S*)-*tert*-Butoxycarbonyl- L-proline (15761-39-4) **83**, 70
(*S*)-*N*-(*N*-*tert*-Butoxycarbonylprolyl)dihydroisindole (188122-39-6) **83**, 70
N-(*tert*-Butoxycarbonyl)- L-serine methyl ester: L-Serine, *N*-[(1,1-dimethylethoxy)carbonyl]-, methyl ester (9); (2766-43-0), **81**, 77
(*S*)-*N*-(*tert*-Butoxycarbonyl)valine methyl ester: Valine, *N*-[(1,1-dimethylethoxy)carbonyl]-, methyl ester, (*S*)-; (58561-04-9), **80**, 57
(*S*)-*N*-(*tert*-Butoxycarbonyl)valine: Valine, *N*-[(1,1-dimethylethoxy)carbonyl]-; (13734-41-3), **80**, 57
tert-Butyl acetate: Acetic acid, 1,1-dimethylethyl ester; (540-88-5), **81**, 179
n-Butyl acrylate: 2-Propenoic acid, butyl ester; (141-32-2), **80**, 172
(*R*_S)-(+)-*tert*-Butyl *tert*-butanethiosulfinate: 2-Propanesulfinothioic acid, 2-methyl-, *S*-(1,1-dimethylethyl) ester, [*S*(*R*)]-; (67734-35-4) **82**, 157
tert-Butyldichlorophosphine: Phosphonous dichloride, (1,1-dimethylethyl)-; (25979-07-1) **82**, 22
n-BUTYL 2,2-DIFLUOROCYCLOPROPANECARBOXYLATE:
Cyclopropanecarboxylic acid, 2,2-difluoro-, butyl ester; (260352-79-2), **80**, 172
tert-Butyldimethylphosphine)trihydroboron: Boron, [(1,1-dimethylethyl)dimethylphosphine]-trihydro-; (203000-43-5) **82**, 22
tert-Butyldimethylsilyl chloride: Silane, chloro(1,1-dimethylethyl)dimethyl- (9); (18162-48-6), **81**, 157; **83**, 155

- (*tert*-Butyldimethylsilyloxy)acetaldehyde: Acetaldehyde, [[[1,1-dimethylethyl]dimethylsilyl]oxy]-; (102191-92-4) **82**, 34
- 1-(*tert*-BUTYLDIMETHYLSILYLOXY)-8-(METHOXYCARBONYL)-6-METHYLBICYCLO [4.2.0]OCTANE: Bicyclo[4.2.0]octane-7-carboxylic acid, 6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-methyl-, methyl ester, (1*R*,6*R*,7*S*)-rel-; (657428-75-6) **83**, 193
- 1-*tert*-Butyldimethylsilyloxy-2-methyl-1-cyclohexene: Silane, (1,1-dimethylethyl)dimethyl[(2-methyl-1-cyclohexen-1-yl)oxy]-; (20152-33-4) **83**, 193
- (*S*)-4-(*tert*-BUTYLDIMETHYLSILYLOXY)-2-PENTYN-1-OL, **81**, 157
ee determination, **81**, 164
- (*S*)-2-(*tert*-Butyldimethylsilyloxy)propanal: Propanal, 2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, (2*S*)-; (87727-28-4), **81**, 159
- 3-BUTYL-2-FLUORO-1-TOSYLINDOLE: 1*H*-Indole, 3-butyl-2-fluoro-1-[(4-methylphenyl)sulfonyl]-; (195734-36-2) **83**, 111
- 1-(*TERT*-BUTYLIMINO-METHYL)-1,3-DIMETHYL-UREA HYDROCHLORIDE **82**, 59
- tert*-Butyl isocyanide: Propane, 2-isocyano-2-methyl-; (7188-38-7) **82**, 59
- n*-Butyllithium: Lithium, butyl-; (109-72-8) **80**, 160; **81**, 2, 43, 44, 89, 112, 134, 159; **82**, 43, 147
- sec*-Butyllithium: Lithium, (1-methylpropyl)-; (598-30-1), **80**, 46; **82**, 22
- tert*-Butyllithium: Lithium, (1,1-dimethylethyl)-; (594-19-4), **81**, 122
- n*-Butylmagnesium chloride: Magnesium, butylchloro-; (693-04-9), **80**, 111
- Butyl methacrylate: 1-Propenoic acid, 2-methyl-, butyl ester; (97-88-1), **81**, 63
- 1-Butyl-3-methylimidazolium chloride: 1*H*-Imidazolium, 1-butyl-3-methyl-, chloride; (79917-90-1) **82**, 166
- 1-Butyl-3-methylimidazolium tetrafluoroborate: 1*H*-Imidazolium, 1-butyl-3-methyl, tetrafluoroborate (1-); (174501-65-6) **82**, 166
- (5*S*,6*R*)-4-*tert*-BUTYLOXYCARBONYL-5,6-DIPHENYLMORPHOLIN-2-ONE: 4-Morpholinecarboxylic acid, 6-oxo-2,3-diphenyl-, 1,1-dimethylethyl ester, (2*R*-*cis*)-; (173397-90-5), **80**, 18, 31
- (5*R*,6*S*)-4-*tert*-BUTYLOXYCARBONYL-5,6-DIPHENYLMORPHOLIN-2-ONE: 4-Morpholinecarboxylic acid, 6-oxo-2,3-diphenyl-, 1,1-dimethylethyl ester, (2*S*-*cis*)-; (112741-50-1), **80**, 18
- 1-*tert*-BUTYLOXYCARBONYL-4-(9-FLUORENYLMETHYLOXYCARBONYLAMINO)PIPERIDINE-4-CARBOXYLIC ACID: 1,4-Piperidinedicarboxylic acid, 4-[[[(9*H*-fluoren-9-yl)methoxy]-carbonyl]amino]-, 1-(1,1-dimethylethyl)ester; (183673-66-7), **81**, 213
- 1-*tert*-Butyloxycarbonylpiperidine-4-spiro-5'-(1',3'-bis(*tert*-butyloxycarbonyl) hydantoin: 1,3,8-Triazaspiro[4.5]decane-1,3,8-tricarboxylic acid, 2,4-diiso-, tris(1-dimethylethyl)ester; (183673-68-9), **81**, 214
- (*R*)-3-Butyn-2-yl mesylate: 3-Butyn-2-ol, methanesulfonate, (2*R*)-; (121882-95-4) **82**, 43
- anti*-(1*R*)-(1)-Camphorquinone 3-oxime: 1,7,7-Trimethyl-bicyclo[2.2.1]heptane-2,3-dione 3-oxime; (31571-14-9) **82**, 87
- D-(+)-Camphorsulfonic acid: Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1*S*,4*R*)-; (3144-16-9), **80**, 66
- (1*R*)-(+)-Camphor: 1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-one; (464-49-3) **82**, 87

(2-Carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide: Phosphonium, [[2-(methoxycarbonyl)-6-nitrophenyl]methyl]triphenyl-, bromide; (195992-09-7), **80**, 75

Carbon dioxide; (124-38-9), **80**, 46

Carbon monoxide; (630-08-0), **80**, 75, 93

Carbon tetrabromide: Methane, tetrabromo-; (558-13-4), **81**, 1

Carbon tetrachloride: Tetrachloromethane; (56-23-5) **82**, 93

Carbonyldihydridotris(triphenylphosphine)ruthenium(II): Ruthenium, carbonyldihydridotris(triphenylphosphine); (25360-32-1), **80**, 104

Catalytic reduction **82**, 1

Catecholborane: 1,3,2-Benzodioxaborole; (274-07-7) **83**, 24

Cesium carbonate: Carbonic acid, dicesium salt; (534-17-8) **82**, 69

Cesium hydroxide: Cesium hydroxide (CsOH); (21351-79-1), **80**, 38

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Chloride formation **83**, 38

Chloroacetic acid; (79-11-8) **82**, 157

Chloroacetyl chloride: Acetyl chloride, chloro-; (79-04-9), **80**, 200

2-CHLOROACROLEIN DIETHYL ACETAL: 1-Propene, 2-chloro-3,3-diethoxy-; (7575-33-9)

Chlorobenzene: Benzene, chloro-(8,9); (108-90-7), **81**, 64

4-Chlorobenzoic acid methyl ester: Benzoic acid, 4-chloro-, methyl ester; (1126-46-1), **81**, 34

4-Chlorobenzonitrile: Benzonitrile, 4-chloro- (9); (623-03-0), **81**, 64

2-CHLORO-1,3-BIS(DIMETHYLAMINO)TRIMETHINIUM HEXAFLUOROPHOSPHATE: Methanaminium, *N*-[2-chloro-3-(dimethylamino)- 2-propenylidene]-*N*-methyl-, hexafluorophosphate(1-); (249561-98-6), **80**, 207

1-CHLORO-4-(2,2-DICHLORO-1-METHYLVINYL)BENZENE: Benzene, 1-chloro-4-(2,2-dichloro-1-methylethenyl)-; (73644-88-9) **82**, 93

Chlorodimethylsilane; (1066-35-9) **83**, 38

1-Chloro-3-iodobenzene; (625-99-0) **82**, 126

1-CHLORO-3-iodo-5-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)BENZENE: (2-(3-Chloro-5-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; (479411-94-4) **82**, 126

m-Chloroperbenzoic acid; Benzenecarboperoxoic acid, 3-chloro-; (937-14-4), **80**, 207

9-Chloromethylanthracene: Anthracene, 9-(chloromethyl)-; (24463-19-2), **80**, 38

1-(4-Chlorophenyl)ethanone; (99-91-2) **82**, 93

1-(4-Chlorophenyl)ethanone hydrazone; (40137-41-5) **82**, 93

N-Chlorosuccinimide: 2,5-Pyrrolidinedione, 1-chloro-; (128-09-6), **80**, 133

Chlorotitanium triisopropoxide: Titanium, chlorotris(2-propanolato)-, (T-4)-; (20717-86-6), **80**, 111

Chlorotriethylsilane: Silane, chlorotriethyl-; (994-30-9) **83**, 61

Chlorotrimethylsilane: Silane, chlorotrimethyl- (9); (75-77-4) **80**, 172; **81**, 26, 216; **83**, 61

Chromium(III) Cl Complex: Chromium, chloro[(1*R*,2*S*)-2,3-dihydro-1-[[[2-(hydroxy- κ O)-5-methyl-3-tricyclo[3.3.1.1^{3,7}dec-1-yl]phenyl]methyl-ene]amino- κ N]-1*H*-indene-2-olato-(2-)- κ O],(SP-4-4); (231963-76-1) **82**, 34

Cinchonidine: Cinchonane-9-ol, (8*a*, 9*R*)-; (485-71-2), **80**, 38

R-(+)-Citronellal: 6-Octenal, 3,7-dimethyl-, (3*R*)-; (2385-77-5), **80**, 195

Claisen condensation, **81**, 178

(*S*)-COP-Cl: Cobalt, bis[1,1',1'',1'''-(η^4 -1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis(benzene)](di- μ -chlorodipalladium)bis[μ -[(1- η :1,2,3,4,5- η)-2-[(4*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl- κ N3]-2,4-cyclopentadien-1-yl]]di-; (581093-92-7) **82**, 134

Condensation **83**, 97, 103, 209.

Copper(II) acetate monohydrate: Acetic acid, copper(2+) salt, monohydrate; (6046-93-1) **82**, 108

Copper(I) chloride: Copper chloride; (7758-89-6) **82**, 69, 93

Copper(II) chloride: Copper chloride; (7447-39-4) **82**, 22

Copper(I) Iodide: Copper iodide (CuI); (7681-65-4), **80**, 129

Copper-mediated phenol coupling **82**, 69

Copper sulfate pentahydrate; Sulfuric acid copper(2+) salt (1:1), pentahydrate; (7758-99-8) **83**, 184

Cross coupling, **81**, 33; **83**, 31, 45, 103

Cross enyne metathesis, **81**, 1; **83**, 200

Crotonic acid: 2-Butenic Acid; (3724-65-0) **83**, 49

Cuprous bromide-dimethylsulfide complex: Copper, [thiobis(methane)]; (54678-23-8) **82**, 43

Cu(OTf)₂: Methanesulfonic acid, trifluoro-, copper(2+) salt; (34946-82-2) **83**, 5

Cycloaddition, of difluorocarbene, **80**, 172
of dichlorocarbene **83**, 184

[2+2] Cycloaddition, **80**, 160; **83**, 193

[3+2] Cycloaddition, **80**, 144

[4+3] Cycloaddition, **83**, 61

Cyclocondensation **82**, 170; **83**, 49, 97, 103, 209

Cyclohexanecarboxaldehyde; (2043-61-0), **81**, 26

Cyclohexene; (110-83-8), **81**, 43

Cyclohexylamine: Cyclohexanamine; (108-91-8), **80**, 93

Cycloisomerization, **83**, 103

Cyclooctadienyl)ruthenium dichloride polymer, **81**, 178

(Cyclooctadienyl)ruthenium dichloride polymer-(*R*)-BINAP catalyst, [Et₂NH₂]⁺[Ru₂Cl₅(BINAP)₂]⁻, **81**, 178

Cyclopentadiene: 1,3-Cyclopentadiene (8,9); (542-92-7), **81**, 171; **82**, 1

2-Cyclopenten-1-one; (930-30-3), **80**, 144

2-CYCLOPENTYLACETOPHENONE: Ethanone, 2-cyclopentyl-1-phenyl-; (23033-65-0), **81**, 121

Cyclopentylmagnesium chloride: Magnesium, chlorocyclopentyl-; (32916-51-1), **80**, 111

Cyclopropane synthesis, **80**, 111; **81**, 15; **83**, 184

Cyclopropene synthesis, **80**, 145

Cyclopropanol synthesis, **80**, 111

Cyclopropylamine synthesis, **81**, 14

(-)-Cytisine: 1,5-Methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one, 1,2,3,4,5,6-hexahydro-, (1*R*,5*S*)-; (485-35-8) **83**, 141

1-Decanol: 1-Decanol (9); (112-30-1) **82**, 80

Decanal: Decanal (8,9); (112-31-2) **82**, 80

3,6-DIACETYL-9,10-DIMETHOXYPHENANTHRENE: Ethanone, 1,1'-(9,10-dimethoxy-3,6-phenanthrenediyl)bis-; (310899-08-2), **80**, 227, 233

1,2:5,6-DIANHYDRO-3,4-*O*-ISOPROPYLIDENE-L-MANNITOL: L-MANNITOL, 1,2:5,6-DIANHYDRO-3,4-*O*-(1-METHYLETHYLIDENE)-; (153059-37-1), **81**, 140

1,4-Diazabicyclo[2.2.2]octane (DABCO); (280-57-9) **83**, 1

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU): Pyrimido[1,2-*a*]azepine, 2,3,4,6,7,8,9,10-octahydro-; (6674-22-2) **82**, 134

Deuterium oxide: Water-d₂; (7789-20-0), **80**, 120

Diazo transfer reaction, **80**, 161

Dibenzofuran; (132-64-9), **80**, 46

Dibenzofuran-4,6-dicarbonyl chloride: 4,6-Dibenzofurandicarbonyl dichloride; (151412-73-8), **80**, 46

Dibenzofuran-4,6-dicarboxylic acid: 4,6-Dibenzofurandicarboxylic acid; (88818-47-7), **80**, 46

(*R,R*)-Dibenzofuran-4,6-dicarboxylic acid bis(2-hydroxy-1-phenylethyl)amide: 4,6-Dibenzofurandicarboxamide, *N,N'*-bis[(1*R*)-2-hydroxy-1-phenylethyl]-; (247097-79-6), **80**, 46

(*R,R*)-4,6-DIBENZOFURANDIYL-2,2'-BIS(4-PHENYLOXAZOLINE) (DBFOX/PH): Oxazole, 2,2'-(4,6-dibenzofurandiyl)bis(4,5-dihydro-4-phenyl-, (4*R*,4'*R*)-; (195433-00-2), **80**, 46

Dibenzoyl peroxide: Peroxide, dibenzoyl; (94-36-0), **80**, 75

Dibenzylamine: Benzenemethanamine, *N*-(phenylmethyl)-; (103-49-1), **81**, 18, 204

N,N-DIBENZYL-*N*-(2-ETHENYLCYCLOPROPYL)AMINE: BENZENEMETHANAMINE, *N*-(2-ETHENYLCYCLOPROPYL)-*N*-(PHENYLMETHYL)-; (220247-75-5), **81**, 14

N,N-Dibenzylformamide: Formamide, *N,N*-bis(phenylmethyl)-; (5464-77-7), **81**, 14

Dibenzylideneacetone: 1,4-Pentadien-3-one, 1,5-diphenyl-; (538-58-9), **81**, 56

Dibenzyl phosphate: Phosphoric acid, bis(phenylmethyl) ester; (1623-08-1), **80**, 219

(4,4-Dibromobut-3-enyl)benzene: Benzene, (4,4-dibromo-3-butenyl)-; (119405-97-9), **81**, 1

3,4-Dibromo-2,5-diformylthiophene: 2,5-Thiophenedicarboxaldehyde, 3,4-dibromo-; (25373-20-0) **83**, 209

Dibromo-2,5-dimethoxytetrahydrofuran: Furan, 3,4-dibromotetrahydro-2,5-dimethoxy-; (91468-55-2) **82**, 179

Di-*tert*-butyl dicarbonate: Dicarboxylic acid, bis(1,1-dimethylethyl) ester; (24424-99-5), **80**, 18; **81**, 215; **83**, 70

Dibutyl phosphate: Phosphoric acid, dibutyl ester (8,9); (107-66-4), **81**, 226

2,3-Dibromo-1,1,4,4-tetramethoxybutane: Butane, 2,3-dibromo-1,1,4,4-tetramethoxy-; (25537-21-7) **82**, 179

4,4'-Di-*tert*-butyl-2,2'-bipyridine (dtbpy): 4,4'-Bis(1,1-dimethylethyl)-2,2'-bipyridine; (72914-19-3) **82**, 126

Di-*tert*-butyl disulfide: Disulfide, bis(1,1-dimethylethyl); (110-06-5) **82**, 157

3,5-Di-*tert*-butyl salicylaldehyde: Benzaldehyde, 3,5-bis(1,1-dimethylethyl)-2-hydroxy-; (37942-07-7) **82**, 157

DIBUTYL 3,4,6-TRI-*O*-BENZYL-2-*O*-PIVALOYL-D-GLUCOPYRANOSYL PHOSPHATE: β-D-GLUCOPYRANOSE, 3,4,5-TRIS-*O*-(PHENYLMETHYL)-, 1-(DIBUTYL PHOSPHATE) 2-(2,2-DIMETHYLPROPANOATE); (223919-63-7), **81**, 225

1,3-Dichloroacetone: 2-Propanone, 1,3-dichloro-; (534-07-6), **80**, 144

Di-μ-chloro-bis(1,5-cyclooctadiene)diiridium(I): Iridium, di-μ-chlorobis[(1,2,5,6-η)-1,5-cyclooctadiene]di-; (12112-67-3) **82**, 55

- 1,1-Dichloro-(3*S*)-(*tert*-butyldimethylsilyloxy)-2-butanol *p*-toluenesulfonate: 2-Butanol, 1,1-dichloro-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, 4-methylbenzene sulfonate, (3*S*)-; (329914-17-2), **81**, 159
- Di- μ -chloro-dichlorobis(η^5 -pentamethylcyclopentadienyl)diiridium [Cp*IrCl₂]₂ Iridium, di- μ -chlorodichlorobis[(1,2,3,4,5- η)-1,2,3,4,5-pentamethyl-2,4-cyclopentadien-1-yl]di-; (12354-84-6) **83**, 217
- Dichlorodicyclopentadienylvanadium; Vanadium, dichlorobis (η^5 -2,4-cyclopentadien-1-yl)-; (12083-48-6), **81**, 26
- 1,1-Dichloro-2-ethoxycyclopropane; cyclopropane, 1,1-dichloro-2-ethoxy-; (7363-99-7) **83**, 184
- Dicobalt octacarbonyl: Cobalt, di- μ -carbonylhexacarbonyl di-, (Co-Co); (10210-68-1), **80**, 93
- 1,3-Dicyclohexylcarbodiimide: Cyclohexanamine, *N,N'*-methanetetraylbis-; (538-75-0), **80**, 219; **83**, 70
- dl*-1,2-DICYCLOHEXYLETHANEDIOL: 1,2-ETHANEDIOL, 1,2-DICYCLOHEXYL- (9); (92319-61-4) **81**, 26
- Dicyclopentadiene: 4,7-Methano-1*H*-indene, 3*a*,4,7,7*a*-tetrahydro-; (77-73-6), **81**, 173
- (*Z*)-1,2-DIDEUTERIO-1-(TRIMETHYLSILYL)-1-HEXENE: Silane, (1,2-dideuterio-1-hexenyl)trimethyl-, (*Z*)-; **80**, 120
- Diels-Alder reaction, **80**, 133, 234; **81**, 171; **82**, 1
- 1, 3-Diene synthesis, **81**, 1; **83**, 200
- 2,2-DIETHOXY-1-ISOCYANOETHANE **82**, 18
- Diethylaminosulfur trifluoride (DAST): Sulfur, (*N*-ethylethanaminato)trifluoro-, (T-4); (38078-09-0), **80**, 46
- Diethylaminotrimethylsilane: Silanamine, *N,N*-diethyl-1,1,1-trimethyl-; (996-50-9), **80**, 195
- Diethyl azodicarboxylate: Azodicarboxylic acid diethyl ester; (1972-58-3), **81**, 142
- Diethylzinc; (557-20-0) **83**, 5, 88, 177
- DIFLUOROCARBENE REAGENT, **80**, 172
- o*-(1,1-Difluorohex-1-en-2-yl)aniline: Benzenamine, 2-[1-(difluoromethylene)pentyl]-; (134810-59-6) **83**, 111
- o'*-(1,1-Difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide: Benzenesulfonamide, *N*-[2-[1-(difluoromethylene)pentyl]phenyl]-4-methyl-; (195734-33-9) **83**, 111
- (2*R*,5*R*)-(+)-*trans*-Dihydrocarvone: (2*R*,5*R*)-2-Methyl-5-(1-methylethenyl)-cyclohexanone; (5948-04-9) **82**, 108
- DIBAL-H (Diisobutylaluminum hydride): Aluminum, hydrobis (2-methylpropyl)- (9); (1191-15-7), **80**, 177; **81**, 157,158; **82**, 43
- Diisopropylamine: 2-Propanamine, *N*-(1-methylethyl)-; (109-72-8), **81**, 159
- Diisopropylethylamine: 2-Propanamine, *N*-ethyl-*N*-(1-methylethyl)-; (7087-68-5) **80**, 207; **81**, 216; **82**, 170
- 1,2,4,5-DI-*O*-ISOPROPYLIDENE-D-erythro-2,3-HEXODIULO-2,6-PYRANOSE: β -D-erythro-2,3-Hexodiulo-2,6-pyranose, 1,2,4,5-bis-*O*-(1-methylethylidene)-; (18422-53-2), **80**, 1, 9
- 1,2,4,5-Di-*O*-isopropylidene- β -D-fructopyranose: β -D-Fructopyranose, 1,2,4,5-bis-*O*-(1-methylethylidene)-; (25018-67-1), **80**, 1
- 1,2,3,4-Di-*O*-isopropylidene- α -D-galactopyranose: α -D-Galactopyranose, 1,2,3,4-bis-*O*-(1-methylethylidene)-; [4064-06-6], **81**, 226
- 1,4:5,8-Dimethanododecahydroanthracene-9,10-dione: 1,4:5,8-Dimethanoanthracene-9,10-dione, dodecahydro-, (1*a*,4*a*,4*aa*,5*b*,8*b*,8*ab*,9*aa*,10*ab*)-; (2065-48-7) **82**, 1

1,4:5,8-Dimethano-1,2,3,4,5,6,7,8-octahydroanthracene-9,10-diol: 1,4:5,8-Dimethanoanthracene-9,10-diol, 1,2,3,4,5,6,7,8-octahydro-, (1a,4a,5b,8b)-; (130778-68-6) **82**, 1

1,4:5,8-Dimethano-1,4,4a,5,8,8a,9a,10a-octahydroanthracene-9,10-dione: 1,4:5,8-Dimethanoanthracene-9,10-dione, 1,4,4a,5,8,8a,9a,10a-octahydro-, (1R,4S,4aR,5S,8R,8aS,9aS,10aR)-; (78548-82-0) **82**, 1

1,4:5,8-dimethano-1,2,3,4,5,6,7,8-octahydro-9,10-1,4:5,8-Dimethano-1,2,3,4,5,6,7,8-octahydro-9,10-dimethoxy-anthracene: 1,4:5,8-Dimethanoanthracene, 1,2,3,4,5,6,7,8-octahydro-9,10-dimethoxy-, (1R,4S,5S,8R)-; (322733-47-1) **82**, 1

Dimethoxyanthracenium Hexachloroantimonate **82**, 1

4,4-Dimethoxybut-2-ynal: 2-Butynal, 4,4-dimethoxy-; (124744-10-1) **82**, 179

2,5-Dimethoxy-2,5-dihydrofuran: Furan, 2,5-dihydro-2,5-dimethoxy-; (332-77-4) **82**, 179

1,2-Dimethylaminoethane: Ethane, 1,2-dimethoxy-; (110-71-4), **80**, 93

Dimethoxymethane: Methane, dimethoxy-; (109-87-5), **80**, 9

9,10-DIMETHOXYPHENANTHRENE: Phenanthrene, 9,10-dimethoxy-; (13935-65-4), **80**, 227

2,2-Dimethoxypropane: Propane, 2,2-dimethoxy-(9); (77-76-9), **80**, 1; **81**, 141; **82**, 75

1,1-Dimethoxy-2-propanone: α,α -Dimethoxyacetone; (6342-56-9) **83**, 61

2,5-Dimethoxytetrahydrofuran: Furan, tetrahydro-2,5-dimethoxy-; (696-59-3) **83**, 103

4-(Dimethylamino)pyridine (DMAP): 4-Pyridinamine, *N,N*-dimethyl-; (1122-58-3), **80**, 177; **81**, 78, 217

Dimethyl biphenyl-4,4'-dicarboxylate: [1,1'-Biphenyl]-4,4'-dicarboxylic acid, dimethyl ester; (792-74-5), **81**, 81

(6R)-(+)-1,6-Dimethylcyclohex-2-en-1-ol: *trans*-1,6-Dimethyl-2-Cyclohexen-1-ol; (114644-29-0), *cis*-1,6-Dimethyl-2-Cyclohexen-1-ol; (114644-28-9) **82**, 108

(R)-(+)-3,4-DIMETHYLCYCLOHEX-2-EN-1-ONE: ((R)-(+)-3,4-Dimethyl-2-cyclohexen-1-one) (10463-42-0) **82**, 108

3,4-DIMETHYLCYCLOPENT-2-ENONE: 3,4-Dimethyl-2-cyclopenten-1-one; (30434-64-1) **83**, 49

2-(5,5-DIMETHYL-1,3,2-DIOXABORINAN-2-YL)BENZOIC ACID ETHYL ESTER: BENZOIC ACID, 2-(5,5-DIMETHYL-1,3,2-DIOXABORINAN-2-YL)-, ETHYL ESTER; (346656-34-6), **81**, 134

cis-5-(5,5-DIMETHYL-1,3-DIOXAN-2-YLIDENE)HEXAHYDRO-1(2H)-PENTALENONE, **80**, 144

N,N-Dimethylformamide: Formamide, *N,N*-dimethyl-; (68-12-2), **80**, 46, 200

2,5-Dimethylfuran; (625-86-5) **83**, 61

(Z)-1,1-Dimethyl-1-heptenylsilanol: Silanol, (1Z)-1-heptenyl dimethyl-; (261717-40-2), **81**, 42

N,O-Dimethylhydroxylamine hydrochloride: Methanamine, *N*-methoxy-, hydrochloride; (6638-79-5) **82**, 147

6,6-DIMETHYL-1-METHYLENE-4,8-DIOXASPIRO[2.5]OCTANE: 4,8-Dioxaspiro[2.5]octane, 6,6-dimethyl-1-methylene; (122968-05-2), **80**, 144

(Z)-3,7-DIMETHYL-2,6-OCTADIEN-1-AL (NERAL): (2Z)-3,7-Dimethyl-2,6-octadienal; (106-26-3) **83**, 18

(Z)-3,7-Dimethyl-2,6-octadien-1-ol (nerol); (106-25-2) **83**, 18

3R,7-DIMETHYL-2-(2-OXOBUTYL)-6-OCTENAL: 6-Octenal, 3,7-dimethyl-2-(3-oxobutyl)-, (3R)-; (131308-24-2), **80**, 195

N,N-Dimethyl-3-phenylpropionamide: Benzenepropanamide, *N,N*-dimethyl-; (5830-31-9) **82**, 188

N,N-Dimethyl-3-phenylpropylamine: Benzenepropanamine, *N,N*-dimethyl-; (1199-99-1) **82**, 188

2,2-Dimethyl-propanedioyl dichloride : Propanedioyl dichloride, dimethyl-; (5659-93-8) **83**, 97

2-(2',2'-DIMETHYLPROPOXY)-2,3-DIHYDRO-1*H*-INDENE; 1*H*-Inden-2-ol, 2,3-dihydro-; (4254-29-9)

Dimethyl sulfate: Sulfuric acid, dimethyl ester; (77-78-1), **80**, 227; **82**, 1

1,3-Dimethylurea: Urea, *N,N'*-dimethyl-; (96-31-1) **82**, 59

Diol synthesis, **81**, 26

Dioxane: 1,4-Dioxane; (123-91-1) **82**, 99

1,4-DIOXENE: (2,3-Dihydro-1,4-dioxin) (543-75-9) **82**, 99

DIPHENYL DISULFIDE: Disulfide, diphenyl; (882-33-7), **80**, 184

(1*S*,2*R*)-1,2-Diphenyl-2-hydroxyethylamine: Benzeneethanol, β -amino- α -phenyl-, (α *R*, β *S*)-rel-; (23412-95-5), **80**, 18

(1*R*,2*S*)-1,2-Diphenyl-2-hydroxyethylamine: Benzeneethanol, β -amino- α -phenyl-, (α *S*, β *R*)-; (23364-44-5), **80**, 18

N-(Diphenylmethylene)glycine *tert*-butyl ester: Glycine, (diphenylmethylene)-, 1,1-dimethylethyl ester; (81477-94-3), **80**, 38

P,P-Diphenylphosphinic amide; (5994-87-6) **83**, 5

Diphosphine Ligands **82**, 22

Directed metallation, **81**, 134

Disodium ethylenediaminetetraacetate: Glycine, *N,N'*-1,2-ethanediylbis[*N*-(carboxymethyl)-, disodium salt; (139-33-3), **80**, 9

Disperse Red 1; Ethanol, 2-[ethyl[4-[4-nitrophenyl]azo]phenyl]amino-; (2872-52-8), **81**, 235

DITHIENO[3,2-*b*:2',3'-*d*]THIOPHENE; (593-75-7) **83**, 209

Dithieno[3,2-*b*:2',3'-*d*]thiophene-2,6-dicarboxylic acid; (502764-53-6) **83**, 209

Dithieno[3,2-*b*:2',3'-*d*]thiophene-2,6-dicarboxylic acid diethyl ester; (502764-52-5) **83**, 209

Dodecylbenzenesulfonic acid; (27176-87-0) **83**, 170

4-Dodecylbenzenesulfonyl azide: Benzenesulfonyl azide, 4-dodecyl-; (79791-38-1), **80**, 160

(*R,R*)-Me-DuPHOS: Phospholane 1,1'-(1,2-phenylene)bis[2,5-dimethyl-, [2*R*-[1(2'*R**,5'*R**)*2a*,5*b*]]-]; (147253-67-6) **83**, 1

Electrophilic aromatic substitution, **80**, 228; **81**, 98; **82**, 30

Electrophilic bromination **82**, 30

Enol silane synthesis, **80**, 233; **83**, 61, 193

Epoxide synthesis, **80**, 9; **81**, 140; **83**, 162

Ester hydrolysis, **81**, 34

Esterification, **81**, 3, 235; **83**, 49, 70.

Ethenone, (triphenylphosphoranylidene)-; (15596-07-3) **82**, 140

ETHYL 4-AMINO BENZOATE: BENZOIC ACID, 4-AMINO-2, ETHYL ESTER; (94-09-7), **81**, 188

Ethyl benzoate: Benzoic acid ethyl ester; (93-89-0), **81**, 134

Ethyl bromoacetate: Acetic acid, bromo-, ethyl ester; (105-36-2), **80**, 18

(*S*)-Ethyl 2-(*tert*-butyldimethylsilyloxy)lactate: Propanoic acid, 2-[[[(1,1-dimethylethyl)dimethyl]oxy], ethyl ester; (106513-42-2), **81**, 157

Ethyl (1'*R*,2'*S*)-*N-tert*-butyloxycarbonyl-*N*-(1',2'-diphenyl-2'-hydroxyethyl) glycinate: Glycine, *N*-[(1,1-dimethylethoxy)carbonyl]-*N*-(2-hydroxy-1,2-diphenylethyl)-, ethyl ester, [*S*-(*R**,*S**)]-; (112741-73-8), **80**, 18

Ethyl (1'*S*,2'*R*)-*N*-*tert*-butyloxycarbonyl-*N*-(1',2'-diphenyl-2'-hydroxyethyl)glycinate: Glycine, *N*-[(1,1-dimethylethoxy)carbonyl]-*N*-(2-hydroxy-1,2-diphenylethyl)-, ethyl ester, [*R*-(*R**,*S**)]-; (112741-70-5), **80**, 18
 ETHYL 3-CHLORO-3-PHENYLPROPANOATE: Benzenepropanoic acid, β -chloro-, ethyl ester; (77085-24-6) **83**, 38
 Ethyl (1'*S*,2'*R*)-*N*-(1',2'-diphenyl-2'-hydroxyethyl)glycinate: Glycine, *N*-(2-hydroxy-1,2-diphenylethyl)-, ethyl ester, [*R*-(*R**,*S**)]-; (100678-82-8), **80**, 18
 Ethyl (1'*R*,2'*S*)-*N*-(1',2'-diphenyl-2'-hydroxyethyl)glycinate: Glycine, *N*-(2-hydroxy-1,2-diphenylethyl)-, ethyl ester, [*S*-(*R**,*S**)]-; (112835-62-8), **80**, 18
 Ethyl 3-hydroxy-3-phenylpropanoate: Benzenepropanoic acid, β -hydroxy-, ethyl ester; (5764-85-2) **83**, 38
 Ethylene: Ethene; (74-85-1), **81**, 4
 purification of, **81**, 8
 reaction apparatus for addition of, **81**, 9
 Ethylenediaminetetraacetic acid (EDTA): Glycine, *N,N'*-1,2-ethanediybis[*N*-(carboxymethyl)-];(60-00-4), **80**, 9
 (*S*)-Ethyl lactate: Propanoic acid, 2-hydroxy-, ethyl ester, (2*S*)-; (687-47-8), **81**, 157
 Ethyl 2-mercaptoacetate: Acetic acid, mercapto-, ethyl ester; (623-51-8) **83**, 209
 Ethyl methacrylate: 2-Methyl-2-propenoic acid, ethyl ester; (97-63-2) **83**, 24
 Ethyl 4-nitrobenzoate: Benzoic acid, 4-nitro-, ethyl ester (9); 99-77-4), **81**, 188
 Ethylphosphonic acid bis-(2,2,2-trifluoroethyl) ester: Phosphonic acid, ethyl-, bis(2,2,2-trifluoroethyl) ester; (650-16-8) **82**, 147
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 ETHYL 2-[(2,6,6-TRIMETHYLBICYCLO[3.1.1]HEPT-3-YL)METHYL]PROPENOATE; (183623-93-0) **83**, 24
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Lithium bis(trimethylsilyl)amide; Lithium hexamethyldisilazide: Silanamine, 1,1,1-trimethyl-*N*-(trimethylsilyl)-, lithium salt; (4039-32-1), **80**, 31, 160; **81**, 179

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Meldrum's acid: 1,3-Dioxane, 4,6-dione, 2,2-dimethyl-; (2033-24-1), **80**, 133

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2-Mesitylmagnesium bromide: Magnesium, bromo(2,4,6-trimethylphenyl)-; (2633-66-1) **83**, 131

Mesyl chloride: Methanesulfonyl chloride; (124-63-0) **82**, 43

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(Methoxycarbonylmethylene)triphenylphosphorane: Phosphonium, triphenyl-, 2-methoxy-2-oxoethylide; (21204-67-1) **82**, 140

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N-Methoxy-*N*-methylcarbonyl chloride: Carbamic chloride, methoxymethyl-; (30289-28-2) **82**, 147

[1-(METHOXYMETHYLCARBAMOYL)ETHYL]PHOSPHONIC ACID BIS-(2,2,2-TRIFLUOROETHYL) ESTER: Phosphonic acid, [2-(methoxymethylamino)-1-methyl-2-oxoethyl]-, bis(2,2,2-trifluoroethyl) ester; (448219-33-8) **82**, 147

4-Methoxyphenacyl bromide; Ethanone, 2-bromo-1-(4-methoxyphenyl)-; (2632-13-5), **81**, 105

4-Methoxyphenethyl alcohol: Benzeneethanol, 4-methoxy-; (702-23-8), **81**, 195

4-Methoxyphenol: Phenol, 4-methoxy-; (150-76-5) **82**, 55, 69

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4-(4-METHOXYPHENYL)-2-PHENYL-1*H*-IMIDAZOLE: 1*H*-IMIDAZOLE, 4-(METHOXYPHENYL)-2-PHENYL-; (53458-08-5), **81**, 105

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1-Methoxy-4-vinylbenzene **82**, 55

Methyl acrylate: 2-Propenoic acid, methyl ester; (96-33-3), **80**, 38; **83**, 162, 193

Methyl 2-bromomethyl-3-nitrobenzoate: Benzoic acid, 2-bromomethyl-3-nitro-, methyl ester; (98475-07-1), **80**, 75

Methyl *tert*-butyl ether; Propane, 2-methoxy-2-methyl-; (1634-04-4), **81**, 195; **82**, 69

2-Methyl-3-butyn-2-ol: 3-Butyn-2-ol, 2-methyl-; (115-19-5), **80**, 93

(*R*)-(+)-6-Methylcyclohex-2-en-1-one: (6*R*)-6-Methyl-2-cyclohexen-1-one; (62392-84-1) **82**, 108

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N-Methyldicyclohexylamine: Cyclohexanamine, *N*-cyclohexyl-*N*-methyl-; (7560-83-0), **81**, 63, 64

(*S*)-1-Methyl-2-[(dihydroisoindol-2-yl)methyl]pyrrolidine (159497-37-7) **83**, 70

Methyl 2-ethenyl-3-nitrobenzoate: Benzoic acid, 2-ethenyl-3-nitro-, methyl ester; (195992-04-2), **80**, 75

(4*S*)-(1-METHYLETHYL)-5,5-DIPHENYLOXAZOLIDIN-2-ONE: 2-Oxazolidinone, 4-(1-methylethyl)-5,5-diphenyl-, (4*S*)-; (184346-45-0), **80**, 57

(±)-Methyl glycidate: Oxiranecarboxylic acid, methyl ester; (4538-50-5) **83**, 162

(*S*)-METHYL GLYCIDATE: Oxiranecarboxylic acid, methyl ester, (2*S*)-; (118712-39-3) **83**, 162

Methyl 5-hexenoate: 5-Hexenoic acid, methyl ester; (2396-80-7), **80**, 111

N-Methylimidazole: 1*H*-Imidazole, 1-methyl-; (616-47-7), **81**, 236

METHYL INDOLE-4-CARBOXYLATE: 1*H*-Indole-4-carboxylic acid, methyl ester; (39830-66-5), **80**, 75

Methyl iodide: Methane, iodo-; (74-88-4), **80**, 57, 144

Methyl 4-iodobenzoate: Benzoic acid, 4-iodo-, methyl ester; (619-44-3), **81**, 78

Methyl lithium: Lithium, methyl-; (917-54-4), **81**, 16

Methyl lithium-lithium bromide; (332360-06-2) **82**, 108

Methylmagnesium bromide: Magnesium, bromomethyl-; (75-16-1) **82**, 22

Methyl 2-methyl-3-nitrobenzoate: Benzoic acid, 2-methyl-3-nitro-, methyl ester; (59382-59-1), **80**, 75

METHYL 5-METHYLPYRIDINE-2-CARBOXYLATE: 2-Pyridinecarboxylic acid, 5-methyl-, methyl ester; (260998-85-4), **80**, 133

(-)-Methyl (1*R*,9*R*)-6-Oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-diene-11-carboxylate: 1,5-Methano-2*H*-pyrido[1,2-*a*][1,5]diazocine-3(4*H*)-carboxylic acid, 1,5,6,8-tetrahydro-8-oxo-, methyl ester, (1*R*,5*R*)-; (125109-97-9) **83**, 141

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anti-3-METHYL-1-PHENYL-4-PENTEN-1-OL (205883-12-1)

N-[(4-Methylphenyl)sulfonyl(phenyl)methyl] *P,P*-diphenylphosphinic amide; (701291-86-3) **83**, 5

METHYL PHENYL SULFOXIDE: Benzene, (methylsulfinyl)-; (1193-82-4), **80**, 184

(*R*_S)-(+)-2-METHYL-2-PROPANESULFINAMIDE [*TERT*-BUTANESULFINAMIDE]: 2-Propanesulfinamide, 2-Methyl-, [*S*(*R*)]-; (196929-78-9) **82**, 157

N-Methylpyrrolidinone: 2-Pyrrolidinone, 1-methyl-; (872-50-4), **81**, 34; **82**, 69

4-METHYLPYRROLO[1,2-*a*]QUINOLINE; (796843-24-8) **83**, 103

trans- β -Methylstyrene: Benzene, (1*E*)-1-propenyl-; (873-66-5), **80**, 9
 (*R,R*)-*trans*- β -METHYLSTYRENE OXIDE: Oxirane, 2-methyl-3-phenyl-, (2*R*,3*R*)-; (14212-54-5), **80**, 9
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 Methyl(triphenylphosphine)gold (CH₃AuPPh₃); (23108-72-7) **83**, 55
 Methyl tris(isopropoxy)titanium: Titanium, methyltris(2-propanolato)-, (T-4)-; (18006-13-8), **81**, 16
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 4-NONYLBENZOIC ACID: Benzoic acid, 4-nonyl-; (38289-46-2), **81**, 33
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 Oxygen; (7782-44-7), **80**, 66

 Pd(dba)₂: Palladium, bis[(1,2,4,5- η)-1,5-diphenyl-1,4-pentadien-3-one]- (9); (32005-36-0), **81**, 45, 55

Palladium (II) acetate: Acetic acid, palladium(2+) salt; (3375-31-3), **80**, 75; **81**, 90
 Palladium chloride: Palladium chloride (PdCl₂); (7647-10-1), **81**, 56
 Palladium, dichlorobis(triphenylphosphine)- (PPh₃)₂PdCl₂; (13965-03-2) **83**, 103
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 1-Phenylcyclohexene: Benzene, 1-cyclohexen-1-yl-; (771-98-2), **80**, 9
 (R,R)-1-PHENYLCYCLOHEXENE OXIDE: 7-Oxabicyclo[4.1.0]heptane, 1-phenyl-, (1R,6R)-; (17540-04-4), **80**, 9
 S-Phenyl diazothioacetate: Ethanethioic acid, diazo-, S-phenyl ester; (72228-26-3), **80**, 160
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 (E)-4-(2-PHENYLETHENYL)BENZONITRILE: BENZONITRILE, 4-[(1E)-2-PHENYLETHENYL]- (9); (13041-79-7), **81**, 63
 (S)-1-Phenylethylamine: Benzenemethanamine, α-methyl-, αS)-; (2627-86-3), **80**, 207
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 1-PHENYLHEX-5-EN-3-AMINE: Benzenepropanamine, α-2-propenyl-; (17125-07-4) **83**, 170
 N-PHENYL-5R-HYDROXYMETHYL-2-OXAZOLIDINONE: 2-Oxazolidinone, 5-(hydroxymethyl)-3-phenyl-, (5R); (875080-42-7), **81**, 112
 Phenylmagnesium bromide: Magnesium, bromophenyl-; (100-58-3), **80**, 57; **83**, 31
 N-[(Phenyl)methylene]-P,P-diphenylphosphinic amide: Phosphinic amide, P,P-diphenyl-N-(phenylmethylene)-; (67764-52-7) **83**, 5
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 (R)-4-Phenyl-2-oxazolidinone: 2-Oxazolidinone, 4-phenyl-, (4R)-; (90319-52-1), **81**, 147
 5-PHENYLPENT-2-YN-1-OL: 2-Pentyn-1-ol, 5-phenyl-; (16900-77-9), **81**, 2
 R-4-PHENYL-3-(1,2-PROPADIENY)-2-OXAZOLIDINONE: 2-OXAZOLIDINONE, 4-PHENYL-3-(1,2-PROPADIENYL)-, (4R)-; (256382-50-0), **81**, 147
 (1S)-1-Phenylpropan-1-amine hydrochloride: Benzenemethanamine, α-ethyl-, hydrochloride, (αS)-; (19146-52-2) **83**, 5
 3-Phenylpropionaldehyde: Benzenepropanal; (104-53-0), **81**, 2; **83**, 170
 N-[(1S)-1-Phenylpropyl]-P,P-diphenylphosphinic amide: Phosphinic amide, P,P-diphenyl-N-[(1S)-1-phenylpropyl]-; (106651-15-4) **83**, 5
 3-Phenyl-2-propylthio-2-propen-1-ol, **80**, 190
 3-Phenyl-2-propyn-1-ol: 2-Propyn-1-ol, 3-phenyl-; (1504-58-1), **80**, 190

R-4-Phenyl-3-(2-propynyl)-2-oxazolidinone: 2-Oxazolidinone, 4-phenyl-3-(2-propynyl); (4*R*)-; (256382-74-8), **81**, 147

S-Phenyl thioacetate: Ethanethioic acid, *S*-phenyl ester; (934-87-2), **80**, 160

2-PHENYLTHIO-5-HEPTANOL: 3-Heptanol, 6-(phenylthio); (198778-75-5), **81**, 244

4-PHENYL-3-(TRIFLUOROMETHYL)BUTAN-2-ONE: 2-Butanone, 4,4,4-trifluoro-3-(phenylmethyl)-; (808105-43-3) **83**, 177

Phosphorus oxychloride: Phosphoric trichloride; (10025-87-3), **80**, 200

Photolysis, **81**, 245; **83**, 121

Pinacol: 2,3-Butanediol, 2,3-dimethyl-; (76-09-5), **81**, 89

Pinacolborane: 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane; (25015-63-8) **82**, 126

Pinacolic coupling, **81**, 26

(+)- α -Pinene: (1*R*)-2,6,6-Trimethyl-bicyclo[3.1.1]hept-2-ene; (7785-70-8) **83**, 24

Piperidine-4-spiro-5'-hydantoin: 1,3,8-Triazaspiro [4.5]decane-2,4-dione; (13625-39-3), **81**, 214

4-Piperidone monohydrate hydrochloride: 4-Piperidinone, hydrochloride; (41979-39-9), **81**, 214

Pivaloyl chloride: Propanoyl chloride, 2,2-dimethyl-; (3282-30-2), **81**, 226, 254

Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex: Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complex; (68478-92-2), **81**, 55

cis-Polybutadiene; (40022-03-5) **83**, 200

Potassium *tert*-butoxide: 2-Propanol, 2-methyl-, potassium salt; (865-47-4) **80**, 57, 144; **81**, 141; **82**, 87

Potassium cyanide: Potassium cyanide [K(CN)]; (151-50-8), **81**, 214

Potassium hydroxide; (1310-58-3) **82**, 1, 22, 179

Potassium nitrate; (7757-79-1), **81**, 99

(4*S*, 4*S'*)-2,2'-(PROPANE-2,2-DIYL)BIS(4-ISOPROPYL-4,5-DIHYDROOXAZOLE): 2,2'-(1-methylethylidene)bis[4,5-dihydro-4-(1-methylethyl)-, (4*S*,4'*S'*)-; (131833-92-6)

Propanethiol; (79869-58-2), **80**, 190

Propanoic acid, 2-hydroxy-, ethyl ester, (2*S*)-; (687-47-8), **81**, 157

2-Propanol; (67-63-0) **82**, 10

Propargyl alcohol: 2-Propyn-1-ol; (107-19-7) **83**, 200

Propargyl benzoate: 2-Propyn-1-ol, benzoate; (6750-04-5) **83**, 200

Propargyl bromide: 1-Propyne, 3-bromo-; (106-96-7), **81**, 148

Propargylic alcohol synthesis, **81**, 2, 157

N-(2-Propenyl-4-methylbenzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-2-propenyl-; (50487-71-3), **80**, 93

N-(2-Propenyl)-*N*-(2-propynyl)-4-methylbenzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-2-propenyl-*N*-2-propynyl-; (133886-40-5), **80**, 93

Propiolic acid: 2-Propynoic acid; (471-25-0), **80**, 129

Propyl formate: Formic acid, propyl ester; (110-74-7) **82**, 18

1-(2-(1-Propynyl)phenyl)pyrrole: 1*H*-Pyrrole, 1-[2-(1-propynyl)phenyl]-; (796843-21-5) **83**, 103

Pyridine; (110-86-1), **80**, 93, 177; **81**, 3; **82**, 147

Pyridinium chlorochromate: Chromate(1-), chlorotrioxo-, (T-4)-, hydrogen compound with pyridine (1:1); (26299-14-9), **80**, 1; **82**, 108

4-Pyridinamine, *N,N*-dimethyl- (DMAP); (1122-58-3) **83**, 200

3-PYRIDIN-3-YLQUINOLINE: Quinoline, 3-(3-pyridinyl)-; (96546-80-4), **81**, 89

3-PYRIDYLBORONIC ACID: Boronic acid, 3-pyridinyl-; (1692-25-7), **81**, 89

Pyrophosphate synthesis, **80**, 219

Quinidine: Cinchonan-9-ol, 6'-methoxy-, (9*S*)-; (56-54-2) **82**, 120
Quinine: Cinchonan-9-ol, 6'-methoxy-, (8*a*,9*R*)-; (130-95-0) **82**, 120

Radical cation **82**, 1

Reduction, of alkynes, **81**, 43

of aromatic nitro compounds, **81**, 188

of carbamates **83**, 141

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of esters to aldehydes, **81**, 157

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Regioselective alkylation of aromatic ketones, **80**, 104

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Rhodium(II) acetate dimer: Acetic acid, rhodium(2+) salt; (5503-41-3), **80**, 160

Rhodium(1+), [(2,3,5,6-*h*)-bicyclo[2.2.1]hepta-2,5-diene]bis(methyldi-phenylphosphine)-, tetrafluoroborate(1-); (34664-31-8) **82**, 22

Rhodium, chlorotris(triphenylphosphine)-, (RhCl(PPh₃)₃) (SP-4-2)-; (14694-95-2) **83**, 177

D-RIBONOLACTONE **82**, 75

D-Ribonolactone: D-Ribonic acid, γ -lactone; (5336-08-3) **82**, 75

D-Ribose; (50-69-1) **82**, 75

Rochelle salt: Butanedioic acid, 2,3-dihydroxy-(2*R*,3*R*)-, monopotassium monosodium salt; (304-59-6), **81**, 159

Rose Bengal; (11121-48-5), **80**, 66

Ruthenium, dodecacarbonyltri-, triangulo; (15243-33-1) **82**, 188

Ruthenium-mediated reduction **82**, 10

Ruthenium [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro(phenylmethylene)(tricyclohexylphosphine); (246047-72-3) **83**, 200

RuCl[(1*S*,2*S*)-*p*-TsNCH(C₆H₅)CH(C₆H₅)NH₂](η^6 -*p*-cymene): Ruthenium, [*N*-[(1*S*,2*S*)-2-(amino- κ *N*)-1,2-diphenylethyl]-4-methyl-benzenesulfonamidato- κ *N*]chloro-[(1,2,3,4,5,6- η)-1-methyl-4-(1-methylethyl)benzene]-; (192139-90-5) **82**, 10

Salicyl alcohol: Benzenemethanol, 2-hydroxy-; (90-01-7), **81**, 171

Saponification **83**, 209

Silane, [(2,3-dihydro-1*H*-inden-2-yl)oxy](1,1-dimethylethyl)dimethyl-; (216884-03-6) **83**, 155

Silver carbonate: Carbonic acid, disilver(1+) salt; (534-16-7) **82**, 75

Silylation of alcohols, **81**, 157; **83**, 155

Sodium; (7440-23-5), **80**, 144

Sodium amide: Sodium amide (NaNH₂); (7782-92-5), **80**, 144; **82**, 140

Sodium bicarbonate: Carbonic acid monosodium salt; (144-55-8) **82**, 75

Sodium bisulfite: Sulfurous acid, monosodium salt; (7631-90-5) **82**, 30, 75

Sodium carbonate: Carbonic acid disodium salt; (497-19-8) **82**, 55

Sodium chlorite: Chlorous acid, sodium salt; (7758-19-2), **81**, 195
Sodium dithionite: Dithionous acid, disodium salt; (7775-14-6), **80**, 227
Sodium fluoride: Sodium fluoride (NaF); (7681-49-4), **80**, 172
Sodium hydride: Sodium hydride (NaH); (7646-69-7), **81**, 147
Sodium hydrogen sulfite: Sulfurous acid, monosodium salt; (7631-90-5) **82**, 1
Sodium hypochlorite: Hypochlorous acid, sodium salt (8,9); (7681-52-9), **81**, 195; **82**, 80
Sodium iodide: Sodium iodide (NaI); 7681-82-5, **81**, 77, 121
Sodium metaperiodate: Periodic acid (HIO₄), sodium salt; (7790-28-5), **81**, 171
Sodium methoxide: Methanol, sodium salt; (124-41-4), **80**, 133
Sodium nitrite: Nitrous acid, sodium salt; (7632-00-0), **80**, 133
Sodium tetrafluoroborate; (13755-29-8) **82**, 166
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(–)-Sparteine: 7,14-Methano-2*H*,6*H*-dipyrido[1,2-*a*:1',2'-*e*][1,5]diazocine, dodecahydro-, (7*S*,7*aR*,14*S*,14*aS*)-; (90-39-1) **82**, 22
9-SPIROEPOXY-*endo*-TRICYCLO[5.2.2.0^{2,6}]UNDECA-4,10-DIEN-8-ONE: Spiro[4,7-ethano-1*H*-indene-8,2'-oxiran]-9-one, 3*a*,4,7,7*a*-tetrahydro-; (146924-02-9), **81**, 171
Styrene: Benzene, ethenyl-; (100-42-5), **81**, 65
Sulfenate synthesis, **81**, 244
Sulfide synthesis, **81**, 244
Sulfuryl chloride; (7791-25-5), **81**, 247
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TETRABENZYL PYROPHOSPHATE: Diphosphoric acid, tetrakis(phenylmethyl) ester; (990-91-0), **80**, 219
Tetrabutylammonium bromide: 1-Butanaminium, *N,N,N*-tributyl-, bromide; (1643-19-2), **80**, 227
Tetrabutylammonium fluoride: 1-Butanaminium, *N,N,N*-tributyl-, fluoride; (429-41-4) **83**, 111
Tetrabutylammonium fluoride trihydrate: 1-Butanaminium, *N,N,N*-tributyl, fluoride, trihydrate; (87749-50-6), **81**, 45, 55
Tetrabutylammonium hydrogen sulfate: 1-Butanaminium, *N,N,N*-tributyl-, sulfate (1:1); (32503-27-8), **80**, 9
Tetrabromothiophene; (3958-03-0) **83**, 209
Tetrachloromethane: Methane, tetrachloro-; (56-23-5) **82**, 18
Tetrafluoroboric acid: Borate(1-), tetrafluoro-, hydrogen (8,9); (16872-11-0) **82**, 80
2,3,3*a*,4-TETRAHYDRO-2-[(4-METHYLBENZENE)SULFONYL]CYCLOPENTA-[C]PYRROL-5(1*H*)-ONE: Cyclopenta[*b*]pyrrol-5(1*H*)-one, 2,3,3*a*,4-tetrahydro-1-[(4-methylphenyl)sulfonyl]-; (205885-50-3), **80**, 93
Tetrakis(hydroxymethyl)phosphonium sulfate (“Pyroset-TKOW”): Phosphonium, tetrakis(hydroxymethyl)-, sulfate (2:1); (55566-30-8), **80**, 85
Tetrakis(triphenylphosphine)palladium(0); (14221-01-3) **83**, 45
1-Tetralone: 1(2*H*)-Naphthalenone, 3,4-dihydro-; (529-34-0), **80**, 104
1,1,4,4-Tetramethoxybut-2-yne: 2-Butyne, 1,1,4,4-tetramethoxy-; (53281-53-1) **82**, 179
2-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)INDOLE: 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole; (476004-81-6) **82**, 126

3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine: Pyridine, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-; (329214-79-1), **81**, 89

1,1,3,3,-Tetramethyldisiloxane: Disiloxane, 1,1,3,3,-tetramethyl-; (3277-26-7), **81**, 54

N,N,N',N'-Tetramethylethylenediamine: 1,2-Ethanediamine, *N,N,N',N'*-tetramethyl-; (110-18-9), **80**, 46

2,2,6,6-Tetramethylheptane-3,5-dione: 3,5-Heptanedione, 2,2,6,6-tetramethyl-; (1118-71-4) **82**, 69

2,2,6,6-Tetramethylpiperidine; Piperidine, 2,2,6,6-tetramethyl-; (768-66-1), **81**, 134

2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO): 1-Piperidinyloxy, 2,2,6,6-tetramethyl-; (2564-83-2), **81**, 195; **83**, 18

“Thia-Wolff” rearrangement, **80**, 166

Thioanisole: Benzene, (methylthio)-; (100-68-5), **80**, 184

Thiophenol: Benzenethiol; (108-98-5), **81**, 246

Thionyl chloride; (7719-09-7), **80**, 46

Titanium tetrachloride: Titanium chloride (TiCl₄)(T-4); (7550-45-0), **81**, 16

Titanium tetraisopropoxide: 2-Propanol, titanium (4+)salt; (546-68-9) **80**, 120; **81**, 16

Toluene: Benzene, methyl-; (108-88-3) **82**, 55

p-Toluenesulfonic acid: Benzenesulfonic acid, 4-methyl-; (536-57-2) **83**, 5

p-Toluenesulfonyl chloride: Benzenesulfonyl chloride, 4-methyl-; (98-59-9) **80**, 93, 133; **81**, 77, 159

5-(Tosyloxyimino)-2,2-dimethyl-1,3-dioxane-4,6-dione: 1,3-Dioxane-4,5,6-trione, 2,2-dimethyl-, 5-O-[(4-methylphenyl)sulfonyl]oxime; (215436-24-1), **80**, 133

3,4,6-Tri-*O*-benzyl-D-glucal: D-*arabino*-Hex-1-enitol, 1,5-anhydro-2-deoxy-3,4,6-tris-*O*-(phenylmethyl)-; (55628-54-1), **81**, 225

3,4,6-TRI-*O*-BENZYL-2-*O*-PIVALOYL-β-D-GLUCOPYRANOSYL-(1→6)-1,2:3,4-DI-*O*-ISOPROPYLIDENE-α-D-GALACTOPYRANOSIDE: α-D-Galactopyranose, 6-*O*-[2-*O*-(2,2-dimethyl-1-oxopropyl)-3,4,6-tris-*O*-(phenylmethyl)-β-D-glucopyranosyl]-1,2:3,4-bis-*O*-(1-methylethylidene)-; [219122-26-6], **81**, 226

Tri-*tert*-butylphosphine: Phosphine, tris(1,1-dimethylethyl)-; (13716-12-6), **81**, 55, 65

(*P*)-1,2-Tributylstannyl-1,2-butadiene: Stannane, 1,2-butadienyltributyl-; (202119-26-4) **82**, 43

Tributyltin hydride: Stannane, tributyl-; (688-73-3) **82**, 43

(*E*)-2,2,2-Trichloroacetimidic acid hex-2-enyl ester: Ethanimidic acid, 2,2,2-trichloro-, (2*E*)-2-hexenyl ester; (51479-70-0) **82**, 134

Trichloroacetonitrile; (545-06-2) **82**, 134

(*S*)-2,2,2-TRICHLORO-*N*-(1-PROPYLALLYL)ACETAMIDE: Acetamide, 2,2,2-trichloro-*N*-[(1*S*)-1-ethenylbutyl]-; (611182-43-5) **82**, 134

8-[2-(TRIETHOXSILYL)ETHYL-1-TETRALONE: 1(2*H*)-Naphthalenone, 3,4-dihydro-8-[2-(triethoxysilyl)ethyl]-; (154735-94-1), **80**, 104

Triethoxyvinylsilane: Silane, ethenyltriethoxy-; (78-08-0), **80**, 104

Triethylamine; Ethanamine, *N,N*-diethyl-; (121-44-8) **80**, 18, 46, 75, 85, 161, 233; **81**, 77, 121, 214, 244; **82**, 10, 18, 43, 64, 87, 147, 170, 179; **83**, 200

Triethylborane (1.0M solution in hexanes): Borane, triethyl-; (97-94-9) **83**, 88

Triethylsilane: Silane, triethyl-; (617-86-7), **80**, 93; **83**, 155

Trifluoroethanol: Ethanol, 2,2,2-trifluoro-; (75-89-8), **80**, 184; **82**, 147

2,2,2-Trifluoroethyl *p*-toluenesulfonate: Ethanol, 2,2,2-trifluoro-, 4-methylbenzenesulfonate; (433-06-7) **83**, 111

2,2,2-Trifluoroethyl trifluoroacetate: Acetic acid, trifluoro-, 2,2,2-trifluoroethyl ester; (407-38-5), **80**, 160

Trifluoroiodomethane; (2314-97-8) **83**, 177

Trifluoromethylsulfonic acid: Methanesulfonic acid, trifluoro-; (1493-13-6) **82**, 22

Trifluoromethanesulfonic anhydride; (358-23-6) **82**, 170

Trifluoromethanesulfonimide: Methanesulfonamide, 1,1,1-trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]-; (37595-74-7) **83**, 193

(*S*)-*N*-Trifluoromethylsulfonyl-2-isopropylaziridine: (*S*)-2-(1-Methylethyl)-1-[(trifluoromethyl)sulfonyl]-aziridine; (196520-85-1) **82**, 170

Triisopropyl borate: Boric acid (H_3BO_3), tris(1-methylethyl) ester; (5419-55-6), **81**, 89, 134

1,2:3,4:5,6-Tri-*O*-isopropylidene-*L*-mannitol: *L*-Mannitol, 1,2:3,4:5,6-tris-*O*-(1-methylethylidene)-; (153059-35-9), **81**, 140

Triisopropylsilyl triflate: Methanesulfonic acid, trifluoro-, tris(1-methylethyl)silyl ester; (80522-42-5), **80**, 233

Trimethylacetaldehyde: Propanal, 2,2-dimethyl-; (630-19-3) **83**, 155

Trimethylamine hydrochloride: Methanamine, *N,N*-dimethyl-, hydrochloride; (593-81-7), **81**, 77

Trimethylaluminum; (75-24-1) **82**, 170

Trimethylamine oxide: Methanamine, *N,N*-dimethyl-, *N*-oxide; (1184-78-7)

(*S*)-(+)-2,4,6-TRIMETHYLBENZENESULFINAMIDE: Benzenesulfinamide, 2,4,6-trimethyl-, [*S*]_s-; (607729-50-0) **83**, 131

(*R*_s,1*S*,2*R*)-(–)-2,4,6-Trimethylbenzenesulfinic acid 1-(2,4,6-trimethylbenzenesulfonylamino)-2-indan-2-yl ester: Benzenesulfinic acid, 2,4,6-trimethyl-, (1*S*,2*R*)-2,3-dihydro-1-[[[(2,4,6-trimethylphenyl)sulfonyl]amino]-1*H*-inden-2-yl ester, [*S*]_s]-; (607729-49-7) **83**, 131

2,4,6-Trimethylbenzenesulfonyl chloride; (773-64-8) **83**, 131

3-(2,4,6-Trimethylbenzenesulfonyl)-3,3*a*,8,8*a*-tetrahydro-2*H*-1-oxa-2*λ*⁴-thia-3-azacyclopenta[*a*]inden-2-ol: Indeno[1,2-*d'*]-1,2,3-oxathiazole, 3,3*a*,8,8*a*-tetrahydro-3-[[[(2,4,6-trimethylphenyl)sulfonyl]-, 2-oxide, (2*R*,3*aS*,8*aR*)-; (473554-02-8) **83**, 131

1,6,6-Trimethyl-4,8-dioxaspiro[2.5]oct-1-ene: 4,8-Dioxaspiro[2.5]oct-1-ene, 1,6,6-trimethyl-; (122762-81-6), **80**, 144

(*R*)-4-Trimethylsilyl-3-butyn-2-yl acetate: 3-Butyn-2-ol, 4-(trimethylsilyl)-, acetate; (129571-78-4) **82**, 43

(*R*)-4-Trimethylsilyl-3-butyn-2-yl mesylate: 3-Butyn-2-ol, 4-(trimethylsilyl)-, methanesulfonate, (2*R*)-; (200440-90-0) **82**, 43

(*S*)-4-Trimethylsilyl-3-butyn-2-yl succinate: Butanedioic acid, mono [(1*S*)-1-methyl-3-(trimethylsilyl)-2-propynyl] ester; (375395-73-6) **82**, 43

4-Trimethylsilyl-3-butyn-2-ol: 3-Butyn-2-ol, 4-(trimethylsilyl)-; (6999-19-5); (2*R*)-(121522-26-7); (2*S*)-(12155-27-8) **82**, 43

TRIMETHYLSILYL 2-FLUOROSULFONYL-2,2-DIFLUOROACETATE: Acetic acid, difluoro(fluorosulfonyl)-, trimethylsilyl ester; (120801-75-4), **80**, 172

(*Z*)-1-(Trimethylsilyl)-1-hexene: Silane, 1-hexenyltrimethyl-, (*Z*)-; (52835-06-0), **80**, 120

1-(Trimethylsilyl)-1-hexyne: Silane, 1-hexynyltrimethyl-, (3844-94-8), **80**, 120

Trimethylsilyl triflate: Methanesulfonic acid, trifluoro-, trimethylsilyl ester; [27607-77-8], **81**, 226; **83**, 61

Triphenylphosphine: Phosphine, triphenyl-, (603-35-0), **80**, 75; **81**, 2, 91, 142; **82**, 18; **83**, 111

Triphenylphosphine oxide: Phosphine oxide, triphenyl-, (791-28-6) **82**, 18

(TRIPHENYLPHOSPHORANYLIDENE)KETENE: Phosphonium, triphenyl-, oxoethenylide; (73818-55-0) **82**, 140

Triphosgene: Methanol, trichloro-, carbonate (2:1); (32315-10-9) **82**, 147

Tris(dibenzylideneacetone)dipalladium: Palladium, tris[μ-[(1,2-η:4,5-η)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-; (51364-51-3), **81**, 64, 78

Tris(dibenzylideneacetone)dipalladium(0)-chloroform (1/1): Palladium, tris[μ-[(1,2-η:4,5-η)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-, compound with

trichloromethane (1:1); (52522-40-4) **83**, 111

Tris(hydroxymethyl)phosphine: Methanol, phosphinidynetris-; (2767-80-8), **80**, 85

Tris[2-(2-methoxyethoxy)-ethyl]amine: Ethanamine, 2-(2-methoxyethoxy)-*N,N*-bis[2-(2-methoxyethoxy)ethyl]-; (70384-51-9) **82**, 179

Tris(3-pyridyl)boroxin: Pyridine, 3,3',3''-(2,4,6-boroxintriyl)tris-; (160688-99-3), **81**, 89

Tri-*o*-tolylphosphine: Phosphine, tris(2-methylphenyl)-; (6163-58-2), **81**, 78

2,4,6-Trivinylcyclotriboroxane-pyridine complex: Boron, ethenyl[(ethenylboronic acid-*kO*) bimol. monoanhydridato(2-)] (pyridine)-; (95010-17-6) **83**, 45

Urea hydrogen peroxide: Urea, compd. with hydrogen peroxide (H₂O₂) (1:1); (124-43-6), **81**, 204

(*S*)-Valinol: (2*S*)-2-Amino-3-methyl-1-butanol; (2026-48-4) **82**, 170; **83**, 97

Vanadyl bis-acetylacetonate: Vanadium, oxobis(2,4-pentanedionato- $\kappa O, \kappa O'$)-; (3153-26-2) **82**, 157

Vinamidinium salts, **80**, 203

2'-VINYLACETANILIDE: *N*-(2-Vinylphenyl)acetamide: Acetamide, *N*-(2-ethenylphenyl)-; (29124-68-3) **83**, 45

Vinyl acetate: Acetic acid ethenyl ester; (1008-05-4) **82**, 43, 55

Vinyl ether formation **82**, 55

Vinyl iodide synthesis, **81**, 43

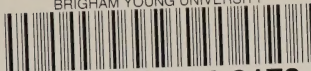
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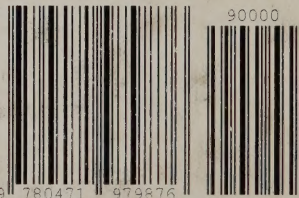
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